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SUBACUTE COMBINED DEGENERATION OF THE CORD: SYMPTOMATOLOGY AND EFFECTS OF LIVER THERAPY.

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THIS article recapitulates, with some modifications, the substance of our paper [24] in the *Newcastle Medical Journal*, of January, 1929.

The detailed tables have been omitted, and a comparative analysis of the cases before and after liver treatment takes their place. Most of the cases have been re-examined, and certain alterations have been necessary, due to changes which have occurred since the patients were last reported on four months ago. In addition, a detailed account of the symptomatology of the sixty-one cases has been included.

While the beneficial effects of liver diet in pernicious anæmia are well recognized, there seems to have been some doubt as to the value of this form of treatment in subacute combined degeneration of the cord. As far as can be gathered from the literature, which is reviewed elsewhere in this paper, no extensive series of cases has previously been reported on, and it would appear that there is considerable difference of opinion on the subject. Because of the doubts existing in this matter, investigations were carried out on all cases of subacute combined degeneration of the cord associated with this hospital since January, 1925; those admitted during the two years prior to the introduction of liver diet were included for purposes of comparison. The series comprises sixty-one cases, of which thirty have been treated by liver.

While our chief object was to determine the effects of liver treatment, an analysis of such a large series of cases of subacute combined degeneration of the cord has been found to contain many points of

interest in the symptomatology of the disease. It is therefore proposed to divide the paper into two distinct parts, dealing firstly with symptomatology, and secondly, with the effects of liver therapy.

I.—Symptomatology.

Before proceeding further, it is desirable to state what evidence has been considered necessary for a diagnosis of subacute combined degeneration.

No case has been included which has not shown definite signs of involvement of either the posterior or lateral columns of the cord, or of both sets of columns. Inco-ordination and ataxia from loss of muscle and joint sensibility, and in addition loss of vibration sensibility, are the signs which have been taken as evidence of posterior column involvement.

The "extensor" type of plantar reflex (Babinski's sign), with or without exaggeration of the deep reflexes and patellar or ankle clonus, have been accepted as evidence of degeneration of the pyramidal fibres of the lateral columns.

Numbness and tingling in the hands and feet, and slighter degrees of anæsthesia in the periphery, although important symptoms, as well as loss of knee and ankle jerks, have not in themselves been regarded as sufficient to warrant a diagnosis of subacute combined degeneration. A certain number of patients with pernicious anæmia exhibit these phenomena, and although we are aware that they probably indicate involvement of the peripheral nerves, or, as some believe, of the posterior columns, we have purposely excluded such cases from this series.

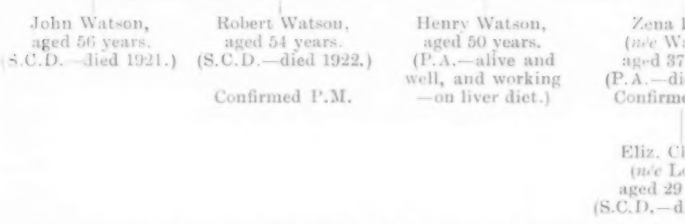
Incidence.—The total number of cases was 61. This shows that the disease is not as rare as some observers have been inclined to believe.

We cannot state definitely whether it is more common in this vicinity than elsewhere; however, a study of the geographical distribution might reveal some interesting facts.

The sexes were involved almost equally, 32 being males and 29 females. The ages varied from 29 to 65, the average age at onset being 45·3 years in males, and 44·3 years in females.

Heredity.—It is well known that cases of pernicious anæmia may occur in several members of a family, and similarly, it has been stated that subacute combined degeneration may have a familial incidence. Such cases have been reported by Hurst [8], Meulengracht [13],

Dorst [4], Johannessohn [9], Liepelt [11], Tscherning [23]. In this connection, the record of the Watson family is interesting, as it shows multiple cases of both diseases co-existing in the one family. Two generations were involved, and in the second generation the disease occurred at an early age and was rapidly fatal.


John Watson, aged 56 years. (S.C.D.—died 1921.)
Robert Watson, aged 54 years. (S.C.D.—died 1922.) Confirmed P.M.
Henry Watson, aged 50 years. (P.A.—alive and well, and working —on liver diet.)
Zena Lowes (*née* Watson), aged 37 years. (P.A.—died 1909.) Confirmed P.M.
Eliz. Charlton (*née* Lowes), aged 29 years. (S.C.D.—died 1926.)

The descendants of this family, nearly thirty in number, are at present being investigated with special regard to gastric analysis and blood changes. Up to the time of writing, the four sons of Henry Watson have been examined; in two of them achlorhydria is present.

Similar investigations are being carried out in another family, in which two sisters have been affected: one died of pernicious anæmia six years ago, whereas the other is now under treatment for subacute combined degeneration.

Onset.—As a rule the patients have been singularly free from previous illnesses. The onset was usually insidious (58 cases). In the three remaining cases, however, the disease began suddenly in the form of an attack of so-called "influenza" with fever and pains in the back and limbs. This was shortly followed by numbness and tingling in the hands and feet and weakness in the legs. A sudden onset was not necessarily associated with a rapid subsequent course.

In 39 cases (63·9 per cent.) the first symptoms were referable to the nervous system:—

Numbness and tingling in 15 cases; it is interesting that in two of these the patient stated that the first symptom was a tingling at the tips of the fingers or toes on flexing the head.

Weakness or stiffness of the legs in 17 cases; occasionally commencing unilaterally (3 cases).

Pains in the back or limbs in 4 cases.

In 10 cases (16·4 per cent.) the earliest symptoms were referable to the alimentary tract. These consisted usually of indigestion and vomiting, and occasionally diarrhœa; in one instance the initial complaint was a sore tongue.

In 12 cases (19·7 per cent.) the first symptoms were attributable to anæmia. These comprised such complaints as pallor, general weakness, shortness of breath, and palpitation. Two of these cases deserve fuller description. Collier [3] states that no case has ever been reported in the literature in which a patient, already under observation for pernicious anæmia, has developed signs and symptoms of combined degeneration of the cord. Piney [20] appears to be of the same opinion. In this series it has occurred definitely in two instances.

Case 16.—S. M., aged 46, female, was admitted on April, 1927, with a three years' history of anæmia and general weakness. Vomiting had occurred during the past year. No numbness or tingling was present, and nothing abnormal was found in nervous system. Gait was not unsteady. Glossitis was present and some pyorrhœa. Blood-films were typical of pernicious anæmia. Red blood-cells numbered 2,370,000, and the colour index was above 1. The white blood-cells were 10,000 per c.mm. Wassermann test was negative. At this period the patient was an uncomplicated case of pernicious anæmia.

Under liver treatment she improved, and at the end of three months felt quite well (August, 1927). She then stopped taking liver because she had difficulty in digesting it in the hot weather, and thought that there was no need to continue with it. About four months after the cessation of liver diet she became much worse. Not only did her pallor return, but she began to complain of "pins and needles" in the extremities, and later became unsteady on her feet, so that she staggered as if drunk. The condition progressed, and finally she lost the use of her legs.

In May, 1928, the patient was re-admitted to hospital, having had no liver diet for ten months. On examination she was grossly anæmic, with a yellow skin. Glossitis was present. The spleen was not palpable. She complained of numbness and tingling in the extremities, of headaches, and was unable to stand. Knee and ankle jerks were present, but the plantar reflexes were not obtained. Some inco-ordination was present, and sensation was much blunted in the legs. Red blood-cells numbered 1,083,000, the hæmoglobin being 20 per cent.

Liver diet was recommenced, with a half-pound of cooked liver daily. The response was rapid, and the reticulocytes rose to 20 per cent. When discharged a month later the red blood-cell count had risen to 4,202,000 per c.mm. and the hæmoglobin to 50 per cent.

After leaving hospital she continued to take about one and three-quarter pounds of liver a week.

On December 6, 1928, she was re-examined. She has gradually improved, has gained in weight, and can now walk without the aid of a stick. The knee-jerks are present and the ankle-jerks absent. The plantar reflexes are doubtful. Co-ordination is good and Romberg's sign negative. There is

slight impairment of joint sense, and vibration sense is deficient below the knees. Sensation to touch and pin-prick is normal. Red blood-cells number 3,510,000, hæmoglobin is 70 per cent. and the colour index 1. White cells are 6,000 per c.mm.

The course of events in this case may be divided into four stages :—

(1) A stage of pernicious anæmia without any symptoms or signs of involvement of the spinal cord.

(2) Rapid remission of the anæmia with liver treatment.

(3) Relapse of the disease following cessation of the liver diet, with the development of subacute combined degeneration of the cord.

(4) Gradual improvement of both blood and nervous phenomena after a further course of liver treatment.

The following case is another interesting example :—

G. R., aged 42, male, was admitted in May, 1925, as a case of pernicious anæmia. He complained of weakness and pallor and of vomiting and diarrhœa. The tongue was clean, with doubtful glossitis, and he was markedly anæmic. The spleen was not palpable. There was total achlorhydria. No abnormal signs were found in the nervous system. Red blood-cells numbered 760,000 per c.mm., and the film was typical. He then had a remission and was well for a few months.

March, 1926.—Readmitted with relapse. He was grossly anæmic, with yellow colour, and complained of vomiting and diarrhœa. Signs of spinal involvement were now beginning to appear. The knee and ankle jerks were exaggerated, and ankle clonus was present. The plantar reflexes were "flexor." There was inco-ordination of the legs. Red blood-cells numbered 688,000, hæmoglobin was 16 per cent., and the colour index 1·3.

After a blood-transfusion his red cell count rose to 3,180,000, and he was discharged.

September 1926, he was again admitted.

After leaving the hospital in April, he had returned to work and had been fairly well until four weeks ago. Vomiting and diarrhœa had recommenced and weakness of the legs developed. His feet were numb with "cotton-wool" feeling and some loss of sensation. There was gross inco-ordination of arms and legs, and Romberg's sign was very marked. The knee and ankle jerks were active : the abdominal reflexes were absent, and the plantar reflexes "flexor." He was very pale with a yellow colour, and was extremely ill. His temperature was 104°, and the pulse 130 per minute. Red blood-cells numbered 950,000 and the white cells 5,600.

He died a week after admission. On autopsy, in addition to the usual changes found in cases of pernicious anæmia, there was extensive degeneration of the posterior columns of the cord.

Symptoms and Signs.

These will be considered under the headings of nervous system, alimentary tract, and blood.

Nervous system.—Numbness and tingling, or "pins and needles" in the extremities, generally of "glove and stocking" distribution, was invariably present.

In addition, various other dysæsthesias were noted, such as girdle sensation and pains in the back and limbs, and a common complaint was that objects felt cold to the skin.

Inco-ordination and ataxia of the lower limbs were present in all cases in which there was sufficient power for these signs to be elicited.

Vibration sense in the tibiæ was impaired or absent whenever noted.

Joint sense in the big toes was also absent or impaired whenever noted, with one exception (Case 5).

Anæsthesia to touch and pin-prick of varying degree was present in the extremities in a fair proportion of cases. In 12 cases the anæsthesia was gross in degree, and in two of these it extended up as far as the waist.

Astereognosis was a feature in 8 cases.

Reflexes: The knee-jerks were absent in 12 cases, and the ankle-jerks in 11 cases. More frequently (27 cases) the deep reflexes were exaggerated even in the very advanced cases just prior to death. The plantar responses were extensor in type in 41 cases. In three fatal cases the plantar responses remained flexor throughout. In one of these an autopsy was performed, and showed involvement of the posterior columns of the cord only.

Athetoid movements occurred in one instance (Case 7). These were slow rigid movements of the hands, which continued incessantly throughout the course of the disease. It is interesting that in this case stimulation of certain areas in the lower limbs produced diffuse pain of thalamic type.

Ocular manifestations occurred in several instances. Some degree of optic atrophy of the primary type was noted in three cases, the diagnosis being made on ophthalmoscopic evidence; nystagmoid movements were present in six and diplopia in two cases, in one of which it was associated with a paralysis of the fourth nerve.

Mental disturbances were present in three cases. In one there was a marked indifference to surroundings, almost amounting to stupor. In the second (Case 21) delusions of persecution were present, whilst the

third (Case 26) suffered from delusional insanity, which necessitated certification.

Disturbances of micturition were encountered in 26 cases. These included difficulty (12 cases), incontinence (11 cases), retention (2 cases), and precipitancy (1 case). It is worthy of note that in all except two of these cases the trouble was accompanied by other evidence of pyramidal involvement (i.e., extensor plantar reflexes).

Alimentary tract.—Symptoms or signs indicating involvement of the alimentary canal were invariably present.

Teeth: No case was encountered with sound teeth. There was either definite pyorrhœa present, or else all or most of the teeth had been extracted. In some cases this had been carried out fifteen to twenty years prior to the onset of the disease.

Hunterian glossitis was noted in 29 cases; of these 18 complained of soreness of the tongue.

Gastro-intestinal symptoms were a common feature. Indigestion was noted in 22 instances; this usually took the form of discomfort after meals, with or without actual pain. Vomiting occurred in 11 of these cases. Diarrhœa was a feature in 3 cases.

Achlorhydria was found in every case in which a fractional test meal was performed (44 out of 61).

Blood.—In every case except six, a definite degree of anæmia (viz., below 4 millions per c.mm.) was present when the patients first came under observation. The average count for all the cases was 2·59 millions, the lowest being 680,000 and the highest 5·6 millions.

It is interesting to note that the three cases who survived for more than two years without liver treatment all had comparatively high counts—viz., 5·6, 4·45, and 3·9 millions per c.mm. respectively.

The colour index was usually, but not invariably, above unity.

The blood-films as a rule were sufficiently typical of pernicious anæmia to be of great value in diagnosis.

When the degree of anæmia is not marked, special methods may be necessary to detect the presence of macrocytosis. These include such means as the Price-Jones curve and the diffraction method.

Yellow discoloration of the skin was present in the cases in which anæmia was at all marked.

The spleen was sufficiently enlarged to be palpable in seven cases.

II.—Effects of Liver Therapy.

A study of the literature shows that opinions vary as to the effects of liver treatment on subacute combined degeneration. Thus, Minot and Murphy [15] describe the effects of this form of treatment in thirty-one cases of pernicious anæmia with prominent symptoms or signs of degeneration of the spinal cord. In nearly all instances numbness and tingling in the extremities had either disappeared or had been much reduced; co-ordination had improved in many, and vibration sense in some cases. Changes in reflexes had remained unaltered. They appear to attribute the improvement to an increase of muscular strength, secondary to the continuous high level of the number of red blood-cells and attach importance to appropriate re-educational exercises.

Koessler and Maurer [10] report two cases, and Bubert [1] and Mason [12] each describe a single case, in which marked improvement in the nervous phenomena occurred on liver diet. Sturgis, Isaacs and Smith [22] found that "improvement in the signs and symptoms of combined posterior and lateral sclerosis of the spinal cord did not parallel the regeneration of the blood, although slow improvement in the neurological condition has frequently followed the combined use of liver extract and physiotherapy."

Wyman Richardson [21] describes fourteen cases with ataxia, of whom eight showed considerable improvement, and four moderate improvement.

On the other hand, Cohen [2] reports a case in which, while there was a distinct general improvement on liver diet, the nervous condition progressed.

Middleton [14] states, "In the majority of cases certain of the lesser evidences of cord involvement, as paræsthesias, weakness and unsteadiness of gait, have been reported improved or relieved; but it is an unusual experience, and scarcely to be anticipated from the underlying pathologic process, that grave cord signs will abate under any form of treatment."

Similarly Ordway and Gorham [19] are of the opinion that advanced cord changes persist almost without exception.

Fried [5], after describing the pathological changes in the cord, concludes: "The serious character of the lesion of the spinal cord in pernicious anæmia, and the peculiarities of tissue repair in the central nervous system render impossible a cure in the spinal cord symptoms under the influence of liver diet. In view of the nature of the lesion, likewise, one may not expect great improvement in the nervous symptoms

even though the anæmia has disappeared, and it is remarkable that any functional improvement at all should occur."

Thirty of this series of sixty-one cases have been treated by feeding on liver. On the whole, the results have been very promising. Where the liver régime has been adequately carried out improvement has occurred, not only in the general condition but also in the nervous phenomena. In a few cases, however, in spite of intensive liver treatment death has occurred, due in most instances to the supervention of some serious complication.

On the other hand, those cases who have discontinued the liver, or have taken it in very small quantities, have become worse or shown but little improvement. Some have improved temporarily and then relapsed when the liver was stopped. The large majority of the cases not treated by liver have died, and in the remainder the disease has taken its usual downward course.

These results are shown in tabular form below :—

	Liver	No liver
Improved	17	0
Not improved, or worse	8	3
Deaths	5	28
Total	30	31

The duration of the disease in these two groups is discussed elsewhere in this paper.

Of the seventeen patients who improved (Cases 1 to 17), eight (Cases 1 to 8) are back at work, and nine, although not working, are much better and able to get about. These patients have been on liver treatment for a period varying from nine to twenty-seven months, the average period being sixteen months. They are all taking 1 to 3 lb. of liver per week.

Of the eight patients (Cases 18 to 25) in whom the symptoms are unchanged, on investigation seven proved to have stopped the liver, or to be taking only small amounts, e.g., ¼ to ½ lb. per week. In the eighth case (Case 18) there was a septic condition of the urinary tract.

Five cases (Cases 26 to 30) died in spite of liver treatment. In at least four of these serious complications were present, and the amount of liver taken was small.

Of thirty-one cases not treated by liver, twenty-eight have died, and three, though still alive, are worse. None has improved. Included in this "non-liver" series are two cases who had had liver or liver extract

in insignificant amounts. One was admitted in a moribund and semi-conscious condition, and although able to take a small quantity of extract on one occasion, died within forty-eight hours. On autopsy, in addition to the usual findings, marked pyelonephritis was present.

The other case was also admitted *in extremis*. There being no extract available at the time, ordinary cooked liver was administered. He only managed to take it in very small quantities on two or three occasions and died within a week of admission.

On account of the grossly inadequate quantities of liver taken in these two cases, it has not been considered justifiable to include them amongst those treated with liver.

The liver-treated cases will now be considered in detail, describing first some examples of improved cases, then those who remained *in statu quo*, and lastly the deaths.

Improved Cases.

Case 1.—G. B., aged 46, male, foreman plumber, was admitted January 9, 1928.

History.—Eighteen months before admission he had an attack of "influenza" which was followed immediately by symptoms of subacute combined degeneration, including numbness and tingling in the hands and feet, and shooting pains in the legs. The tongue was sore at times; his teeth had been extracted. Pallor became noticeable. For eighteen months the numbness increased and he became progressively weaker.

Four months ago walking became difficult, and this trouble increased so that for the two weeks prior to coming into hospital he was unable to walk at all. No previous illnesses and nothing of note in the family history.

Condition before liver treatment.—Marked pallor. Spleen and liver were not palpable. Complete achlorhydria found on fractional test meal. Lower limbs were weak with exaggerated knee-jerks and ankle-jerks, and extensor plantar reflexes. Vibration sense was absent below the knees. There was marked loss of muscle and joint sense, with gross inco-ordination, and Romberg's sign was present. Some impairment of sensation to touch and pin-prick was elicited. Blood-films were typical, and the red blood-cells numbered 2,130,000; hæmoglobin was 40 per cent. and the colour index 0·9. White blood-cells were 9,680 per c.mm.

He was given ½ to 1 lb. of liver daily, and the reticulocytes rose to 13 per cent. on the seventh day of treatment.

After three weeks the red blood-cells amounted to 4,760,000 and hæmoglobin 70 per cent.

There was some diarrhœa in the initial stages, but this soon passed off. He gained a stone in weight (weight now 8½ st.), but on discharge (March 3), he was still unsteady, and the nervous signs were unaltered.

After five months of liver treatment: On May 22 he returned for re-examination. Since leaving hospital he had been taking 1½ lb. of liver per week. A marked improvement was now manifest. His only complaint was some pain in the heels and toes on walking fast, and he expressed a desire to return to his work in the shipyards.

On examination: colour good and now weighed 10 st. 5½ lb. Knee-jerks and ankle-jerks were exaggerated and ankle clonus was present on the left side. The plantar reflexes were now flexor. Subjective and objective sensation was noted as normal. Muscle sense was normal and Romberg's sign negative. Vibration sense was now present in all bones, though still diminished in degree. Red blood-cells numbered 5,437,000 and hæmoglobin was 90 per cent. Achlorhydria was still present.

In June he commenced light work, and by August he was back at the job he held prior to his illness, namely foreman plumber in the shipyards.

After eleven months of liver treatment (i.e., on December 6) the patient was again examined. He had been working for six months now, and felt perfectly well except for an occasional sensation of stiffness in the calves. He continues to take 2 lb. of liver weekly (usually stewed for one and a half to two hours).

Nervous system.—Knee-jerks and ankle-jerks were much exaggerated and patellar clonus was present but no ankle clonus. The plantar reflexes were flexor. Co-ordination was good and Romberg's sign negative. Joint sense was only slightly impaired and there was no anæsthesia to touch or pin-prick. Vibration sense was normal. Red blood-cells numbered 5,060,000, hæmoglobin was 100 per cent. and colour index 1. White blood-cells were 6,000 per c.mm.

After sixteen months (May 6): Apart from some slight numbness of the feet at times, he remains quite fit and is working some fourteen hours a day in the shipyards. He is now taking 1½ lb. of liver per week. Another fractional test meal was performed and still failed to reveal the presence of free hydrochloric acid.

The improvement in this case is particularly striking. As a foreman plumber he works in many parts of a ship during its construction, an occupation requiring perfect co-ordination of movements and a delicate sense of balance. Not only is he practically free from symptoms, but the signs of involvement of the cord have almost disappeared. Particularly noteworthy in this connection is the change of the plantar reflexes from extensor to the flexor type.

Case 2.—T. F., aged 55, male, miner, was admitted February 10, 1928.

History.—Trouble commenced with pain in stomach eight months before admission, and soon after he had difficulty in walking and began to get pale. Later he complained of "pins and needles" in hands and feet. A month before

coming into hospital he was extremely unsteady and could not walk or stand. His tongue was never sore.

He had had no previous illness and his family history was unimportant.

Condition before treatment.—Very pale. Slight glossitis at edges of tongue. Knee and ankle jerks were exaggerated, and ankle clonus was present. Plantar reflexes: right extensor, left doubtful. Romberg's sign was very marked and he was unable to stand without assistance.

Red blood-cells numbered 1,100,000 and hæmoglobin was 34 per cent. The film was typical of pernicious anæmia.

A fractional test meal revealed achlorhydria.

Liver therapy: Half a pound of liver was administered and has been continued since leaving hospital on March 13. He started work eight months later.

After nine and a half months of liver treatment (i.e., on November 28), patient was again examined. He is now working eight and three-quarter hours a day as a miner, and feels only slight tiredness after standing six hours. He has now no numbness or tingling and only some slight temporary paræsthesia in the feet when he gets up in the morning. He has gained a stone and a half in weight.

His colour and general condition is excellent. Knee-jerks and ankle-jerks active and equal. Plantar reflexes: left flexor, right doubtful—probably extensor. Vibration sense present in all bones, but slightly diminished in right leg. Sensation to touch and pin-prick normal. Co-ordination normal. Red blood-cells numbered 5,400,000 and hæmoglobin was 100 per cent.

After thirteen months (i.e., on March 30). Now taking $1\frac{3}{4}$ lb. of liver per week. Improvement is maintained and he has not missed any work. He complains of numbness and tingling at times, especially towards the end of the day's work.

This is another excellent example of subacute combined degeneration treated by liver, in which nervous symptoms have so far regressed as to enable him to earn a living by manual labour.

Case 9.—J. T., aged 39, male, a fitter in shipyards, was admitted on May 12, 1928.

History.—Worked regularly as a fitter until three months before admission, when he began to complain of shortness of breath and palpitation, with indigestion and flatulence, some general weakness and slight cough.

One month later he complained of "pins and needles" in the hands and feet, and noticed that he was very pale with a yellow tinge. One month before admission he was unable to walk. Tongue had not been sore.

Previous history.—Always sallow, but in good health and a regular worker. Operation for hæmorrhoids, 1915. Bilious attacks since boyhood at intervals of three to four months. People used to remark that he often looked jaundiced.

Family history.—Father aged 75 suffers from diabetes. Mother aged 71 is

healthy. Three brothers all healthy. Three sisters, one of whom was operated upon for goitre. Five nephews and nieces, none of whom are anæmic. Four children; one suffers from asthma.

Condition before treatment.—Unable to stand, but can move legs in bed. Gross inco-ordination. Complete analgesia, touch diminished and some loss to heat and cold in legs. Marked numbness and tingling in hands and feet. Cannot write. Astereognosis marked. Knee-jerks and ankle-jerks present. Plantar reflexes doubtful on both sides. Skin yellow, mucous membranes very pale. Hunterian glossitis present. Pyorrhœa present. Spleen and liver not enlarged. Apex of heart in sixth space in nipple line; systolic hæmic murmurs at apex and base. Blood-pressure 130/90. Fractional test meal showed complete achlorhydria. Van den Bergh test gave an indirect positive result and the Wassermann reaction was negative. Red blood-cells numbered 1,200,000: the hæmoglobin was 22 per cent. and the colour index 0·9.

Liver therapy.—From May 19 onwards, liver extract (Oxo) was administered twice a day; after three weeks this was discontinued in favour of cooked liver, of which half a pound was given daily. On the third day of treatment he experienced some difficulty of micturition, without change in the nervous phenomena. A reticulocyte crisis of 17 per cent. occurred and by the fourteenth day the red cells numbered 2·4 millions. Co-ordination and power in the legs and arms were improved and he was now able to turn easily in bed, could shave himself and write. Numbness and tingling had greatly diminished in the legs, but had increased in the hands. The deep reflexes were more easily elicited, and touch and pain sense had returned except in a small area on the back of the thighs.

After seven weeks of liver therapy he attempted to stand but failed, owing to pain and weakness. Tingling in the feet was reduced to "a rough feeling," but there was still some numbness of the back of the thighs. Co-ordination exercises for the feet were commenced. Red cells now numbered 4·1 millions.

By the ninth week he was able to stand without assistance after being steadied. Numbness and slight anæsthesia were still present on the back of the thighs. The knee- and ankle-jerks were active and the plantar reflexes extensor in type. The red cell count reached 7·1 millions, and hæmic murmurs had disappeared. He was discharged a month later.

After six and a half months of liver treatment, i.e., extract for twenty days, 3½ lb. of cooked liver per week for three and a half months, and 1½ lb. per week since, the patient was re-examined (December 6, 1928). Now able to walk two miles a day with ease; uses a stick, but can do without it; slight difficulty in the dark. Does not now complain of shortness of breath: his appetite is good. Only complaint now is a sore patch below left costal margin; this has no relation to food. His tongue, which is not sore, shows slight glossitis at edges. No numbness or tingling, only a "rough" feeling at times. Occasional stiffness in lower parts of calves. Micturition normal.

Nervous system.—Knee-jerks active and equal; ankle-jerks absent. Plantars extensor in type. Abdominal reflexes present. Co-ordination good. No

ataxia. Appreciation of vibration absent in all bones below knees. Joint sense absent in joints of toes, but present in the larger joints. Sensation to pain and touch good. Writing very good. No astereognosis. Red blood-cells numbered 5,000,000 and hæmoglobin was 90 per cent. White blood-cells were 11,000 per c.mm. Colour index was 0·9.

After twelve months (i.e., May, 1929): He has been taking 1½ lb. of liver per week, and is still improving. Slight tingling is present in the feet, but he is quite steady and can walk long distances without the aid of a stick. He is looking for work. Vibration sense has returned although joint sense is still absent in big toes. The deep reflexes are unchanged, but the plantar reflexes have become flexor.

It is interesting to note the rapidity of the improvement in this case. The first definite change in the nervous phenomena, both subjective and objective, was noticed twelve days after the commencement of liver treatment. This rapid improvement may in part be due to the early stage at which liver therapy was commenced, namely, three months after the onset of the disease. This is another instance in which the plantar reflexes, formerly extensor in type, have become flexor.

Case 10.—J. O., aged 49, female, married, was admitted on September 13, 1927.

History.—The trouble started with pain in the back in August, 1926. Weakness of the legs was noticed in December of that year, with numbness and tingling in extremities. Within a few weeks she was unable to walk at all, and took to bed.

While she was in hospital for a month (February 17 to March 17, 1927), the plantar responses were noted as both extensor. The Wassermann reaction was negative. She was discharged unchanged and remained in bed with almost complete paralysis of the legs, which were insensitive up to the hips.

Condition before liver treatment.—Re-admitted September 13, 1927, with complete inability to walk or move her legs, but she had some voluntary power in the individual muscles and could move her toes. Much numbness in hands and legs. Difficulty with micturition. Knee-jerks very sluggish, ankle-jerks absent, and plantar reflexes extensor. Joint sense was grossly deficient. She was anæmic and glossitis was definite. Fractional test meal showed complete achlorhydria. Red blood-cells numbered 2,120,000.

Liver therapy.—Half a pound of liver was given daily, and when discharged on October 28, 1927, she could move her legs well. She continued to take ½ lb. of liver each day for a year, and has taken 2 lb. a week since.

After fourteen months: On December 3, 1928, after fourteen months of liver treatment, patient was re-examined. She had improved immensely and could now walk with the aid of a stick. Colour and general condition were excellent. Pupils were sluggish and the optic discs normal. Legs spastic. The knee-jerks were present, ankle-jerks absent, and the plantar reflexes

extensor. Vibration sense normal, but there was slight blunting of sensation to touch and pin-prick. Co-ordination was poor, and joint sense impaired in legs. Power in legs was good and she could walk with the aid of a stick.

Red blood-cells numbered 5,170,000, hæmoglobin was 100 per cent. and the colour index 1.

After nineteen months there is still further improvement and she can walk better. There are no further changes in the nervous system except that there is less spasticity and more power in the legs. The condition of the blood remains satisfactory.

This case is noteworthy on account of the advanced stage of the disease at which liver treatment was commenced; she had then almost complete paraplegia. She has improved steadily on liver diet and continues to do so.

Unimproved Cases.

These cases will now be described and analysed with a view to ascertaining the possible reasons for the failure of liver treatment.

Case 18.—M. W., aged 61, female. She took 1 to 3 lb. of liver per week for five months; but only ¾ lb. per week for the last twelve months. She improved for a while, but later regressed and is now bedridden. Urine contains much pus and albumin. Incontinence of urine. Red cell count numbered 4·2 millions.

Case 19.—R. R., aged 45, male. He took 2 lb. of liver per week for three months, but none for past seven months. He is now bedridden with incontinence of urine. The red cell count is 4·1 millions.

Case 20.—R. L., aged 45, male: 2½ to 3 lb. of liver per week was administered for fourteen months, but none for the last six weeks. He improved in general condition at first, but rapidly went downhill after stopping liver. Red cell count was 2·2 millions. Plantar responses are now extensor. There is marked pyorrhœa and the urine contains a few pus cells and red corpuscles, and a minute trace of albumin. He is now bedridden, although during the past few months some improvement has occurred in hospital while on full dosage of liver. The red cells number 4·2 millions.

Case 21.—D. A., aged 44, female; ¼ lb. of liver a day was taken for three months, but none for past twelve months. She is still bedridden. Red cells number 2·4 millions.

Case 22.—M. M., aged 54, female; ¼ to ½ lb. of liver per week for twelve months, but none for past two months. She is no longer bedridden, but is still unable to stand and has very little power in her legs. Extensor spasms have ceased and numbness and tingling have diminished. The red cells number 5·2 millions.

Slight improvement has occurred, but as she is still paralysed the case is included amongst those who have remained *in statu quo*.

Case 23.—S. G., aged 44, female; took ½ lb. of liver per week for some months, but none for last few months. She is still bedridden and although her general condition has improved, the nervous symptoms are worse, the legs being weaker and more spastic; flexor spasms are marked. The red cells number 3·2 millions per c.mm.

Case 24.—E. N., aged 42, female, took ½ lb. of liver per week for six weeks, ¼ lb. per week for a short time irregularly, and none for the past few months. She improved markedly at first but relapsed after discontinuing the liver. Red cells numbered 3·7 millions. Recently this patient has been re-examined; she has been taking ¼ lb. liver per day for the past four months, but has not improved. Pyorrhœa is present. Urine contains nothing abnormal. Red cells number 3·2 millions. The spleen is enlarged.

Case 25.—J. A., aged 50, male, took ¼ lb. liver per week for some months, but none for past few months. He improved at first, but has become worse lately. He read of liver treatment in the press, but was not ordered it by doctor. Has lately developed carcinoma of rectum for which he has been operated upon.

From a consideration of the above reports, it will be seen that a constant feature in these cases is the fact that small and irregular amounts of liver were taken. The presence in many of the cases of dental and urinary sepsis is also a notable feature. The influence of these factors on prognosis will be discussed later.

Five cases died in spite of liver treatment. These will now be described in more detail.

Case 26.—R. T., aged 41, male, miner, was admitted on October 3, 1927, as an advanced case of combined degeneration of the cord, with a blood-picture typical of pernicious anæmia. There had been a fifteen months' history of numbness and tingling, with difficulty in walking.

Half a pound of liver was administered daily. On the tenth day the red cell count had increased to 5,570,000, and the reticulocytes to 7 per cent. Some days later he started to cough up purulent sputum, which contained Gram-positive diplococci, but no tubercle bacilli. Moist sounds at bases of lungs, but no impaired resonance. Looked ill. Temperature 101°. Pulse 132. Respirations 24. He soon showed some improvement, and was able to walk before leaving the hospital. Shortly after returning home, although taking ½ lb. of liver a day, he started to get worse. He became pale and yellow, and the delusions (from which, according to his wife, he had been suffering for twelve months) became more intense. Nine weeks after leaving the hospital he was removed to a mental institution, where he died six weeks later. No liver was administered during the latter period.

We cannot account for the fatal termination in this case, unless it was accelerated by the marked and long-standing delusional insanity, and perhaps by his pulmonary condition, the nature of which had never been definitely determined.

Case 27.—K. L., aged 53, female, was admitted on September 24, 1928, as a well-marked case of combined degeneration, having complained of numbness and tingling in the hands and feet for eighteen months, and weakness in the legs for the past four months.

She was given ½ lb. of cooked liver per day: this evoked a reticulocyte crisis, and improvement in her general condition followed. A month later she developed gangrene of the left foot. Severe general convulsions preceded her death, which took place a fortnight after the onset of the gangrene, and during which time the liver had been discontinued.

Death in this case was presumably due to the gangrene. It is not possible to state definitely whether liver administration was the cause of the arterial thrombosis. In this connection, it is noteworthy that two cases of venous thrombosis during liver treatment have come under the notice of the writers.

Case 28.—J. E., aged 65, male, admitted on January 5, 1928, as a very advanced case of combined degeneration, with marked Addisonian anæmia and sphincter trouble. The urine contained albumin and pus.

Administration of B.D.H. liver extract (8 grm. daily: equivalent of ½ lb. of liver) was commenced on January 9. This was continued for six days, and as no improvement occurred, the dose was increased to 16 grm. daily for a further eight days. This treatment had no effect on his blood, not even evoking a reticulocyte crisis. Bed sores developed, the urinary symptoms became worse, and the nervous phenomena progressed, the recti abdominales becoming paralysed.

He died twenty-four days after admission, having been treated with liver extract for fourteen days. During this period he had a total of 88 grm., which is the equivalent of 11 lb. of liver.

On post-mortem examination, apart from evidences of pernicious anæmia and of subacute combined degeneration of the cord, advanced double chronic pyelonephritis and chronic cystitis were found.

The immediate cause of death in this case was apparently the pyelonephritis. The presence of this condition may also have been responsible for the fact that on intensive liver therapy the blood condition did not improve, and that no reticulocyte crisis occurred.

Case 29.—J. E., aged 59, admitted on June 21, 1927, having complained of loss of power in legs with numbness and tingling in the hands and feet for six

months. He became increasingly helpless and developed pyramidal signs and sphincter trouble, which was followed by marked infection of the urinary tract.

Liver diet was advised, but he only managed to take very small quantities at irregular intervals for a short period. Death took place six months after leaving hospital.

In this case the question of the influence of liver diet does not arise to any extent, as, although taken for some months, the amounts were grossly inadequate. The fatal termination, however, was due to the long-standing septic infection of the urinary tract.

Case 30.—G. S., aged 51, male, admitted on August 15, 1928. In January, 1928, complained of pallor and weakness and difficulty in walking, which progressed rapidly.

Small quantities (½ lb. per week) of liver were started shortly afterwards, and continued for three months, during which time there was no change.

In May, administration of liver extract (Boots') was commenced, the dose being one tube per day (the equivalent of ½ lb. of liver). He soon improved in colour, increased in weight, and was able to walk for short distances unaided. A month before admission, however, he suddenly lost the use of his legs completely. In hospital, although the state of his blood was now satisfactory, the nervous system exhibited the picture of an advanced case of subacute combined degeneration of the cord, complicated by sphincter trouble and a bad cough. He was discharged after a week and died a month later, having had no liver during the last month.

With the above patient there appear to have been no serious complications which might have rendered liver therapy unavailing, and thus the failure of the treatment in this case cannot be accounted for.

An analysis of the effects of liver therapy in the seventeen improved cases—and a comparison of their condition before and after treatment.

From what has been said already, it is clear that only by a study of the seventeen improved cases is it possible to determine the effects of a full and prolonged course of liver diet on the signs and symptoms of subacute combined degeneration.

The duration of the disease before treatment was commenced in these cases varied from three months to two years—the average duration being 13·7 months.

The duration of liver treatment varied from eight to twenty-eight months, the average period being 16·6 months.

The condition of these cases before and after treatment will now be considered under the headings of blood, alimentary tract and nervous system, followed by general remarks.

Blood.—Considerable anæmia was present in all the seventeen cases. The lowest red cell count was 1·1 millions per c.mm. and the highest 3·6 millions; the average count being 2·13 millions per c.mm.

(In one instance, Case 15, the red-cell count on admission had been noted as 4·1 millions in our previous paper; it has since been ascertained that this patient had had liver previously at home, and that he had been very anæmic before this.)

As a result of liver treatment, the anæmia disappeared within one to three months. At present, after an average period of 16·6 months of liver diet, the mean red cell count is 4·9 millions.

In every case in which the blood was stained by vital methods during the initial stages of liver administration, a reticulocyte crisis was observed.

No enlargement of the spleen can now be detected in the two cases in which it was formerly palpable.

Alimentary tract.—Soreness of the tongue (six cases) cleared up very rapidly, usually within a few days of commencing the liver diet.

Hunterian glossitis (thirteen cases) was still recognizable after the long periods of liver treatment, but no sign of acute inflammation persisted in any of the cases.

Indigestion with gastric pain (nine cases) and vomiting (four cases) cleared up in a remarkable manner very soon after the commencement of the diet. After an average period of sixteen months' treatment indigestion is present in only two cases, and in these it is not severe.

Transient diarrhœa occasionally occurred during the initial stages of the liver administration.

Many of the patients now complain of constipation, which they attribute, rightly or wrongly, to the liver diet.

Achlorhydria.—Further fractional test meals have been performed in five cases after an average period of 16·7 months of liver treatment. There is still complete achlorhydria in each case.

This confirms the reports of Heath [6], of Minot, Murphy and Stetson [17], and of other observers. However, it is interesting to note that Heeres [7] reports a case in which there was return of free hydrochloric acid in the stomach contents after a period of liver treatment extending over nine months.

Nervous System.

Seventeen cases have already been described which illustrate the beneficial effects of liver diet upon the nervous phenomena of subacute

combined degeneration. It now remains to analyse the effects of the treatment upon individual symptoms and signs in these cases.

Subjective sensations.—Numbness and tingling in the extremities (present in every case of the seventeen) disappeared completely in ten cases, and remained to only a very slight extent in the remainder. A transient increase occurred in a few cases in the early stages (see Case 9).

Lightning pains, girdle sensations and cramps (present in a few cases) cleared up completely.

Incoordination and ataxia with loss of muscle sense in the lower (and occasionally upper) limbs, which were present in every case where sufficient power remained for them to be elicited, and were usually gross, improved considerably in all cases, and in ten cleared up entirely.

Objective sensory loss.—Sensibility to vibration sense was absent or impaired in the tibiæ in every case where it was recorded. It is now present normally in ten of the cases, absent in four, impaired in one, while in two it was not noted.

Joint sense has returned in six of ten cases where it was noted as having been absent.

Cutaneous sensibility to touch and pin-prick, noted as lost or impaired to varying degrees in twelve cases, was found to have become normal in eight of these. In the remaining four, there was but slight blunting of sensibility in small areas of the lower extremity.

Astereognosis, which was noted as being present in two cases, has disappeared completely in one case and partially in the other.

Reflexes.—The knee-jerks were absent in two cases, and exaggerated in the other fifteen. They remain unchanged.

The ankle-jerks were absent in four instances and have not returned. In the remaining thirteen cases these reflexes were exaggerated, and in eleven they still remain so. In the other two cases the ankle-jerks have since disappeared.

Extensor plantar responses, present in nine instances, have changed to flexor type in five cases (Cases 1, 9, 11, 12 and 15). In three of these double extensor responses have become both flexor, and in the other two the change involves one foot only.

Disturbances of micturition.—Either difficulty or incontinence was present in seven cases. In six the trouble has disappeared altogether, whereas the seventh complains of slight difficulty at times.

* * * * *

Before treatment ten of the cases were bedridden, while the

remaining seven had such great difficulty in walking that they were confined to the house.

At the present time eight of them are working; three are miners, while the others are respectively a master plumber in the shipyards, a caretaker, a watchman, a clerk and a housewife.

Three further cases are ready for light employment, while the remaining six, although not yet capable of returning to work, are much better and able to get about.

Progress under liver treatment.—It is interesting to consider the order in which various signs and symptoms are influenced by liver diet.

Improvement in the blood, in the patient's general condition, and in the tongue and gastric symptoms occurs early, and is similar to that which takes place in pernicious anæmia.

As a rule, there is but little apparent improvement in the nervous phenomena during the first two or three months of liver diet. Case 9, however, is an interesting exception to this rule, as improvement in subjective sensations, co-ordination and power occurred within a few weeks, while the red cell count was still about 2,000,000 per c.mm.

Improvement in subjective symptoms and in the ataxia usually occurs first. The return of power is gradual and progressive. Alterations in objective signs only become evident later. The extensor plantar responses may not disappear for long periods, e.g., about twelve months in Case 9, ten months in Case 11, six months in Case 12, five months in Cases 1 and 15. In three other cases the plantar reflexes remain extensor type even after a period of one and a half to two years.

Vibration sense and joint sense may be very late in reappearing. In Case 9, after a year on liver diet, although the plantar reflexes are now flexor in type, and there is marked general improvement, vibration sense has only recently returned, and joint sense in the big toes is still absent.

Prognosis.

Duration of disease.—Prior to the introduction of liver therapy, subacute combined degeneration was always regarded as a progressive and fatal disease. It is interesting to compare the duration of the condition in the "liver" and "non-liver" groups of this series. Of the 31 cases not treated by liver diet, only 3 are still alive, having suffered from the disease for periods of 2·1, 3·7, and 6 years respectively. The remaining 28 were dead within an average period of 14·6 months from the onset of the disease.

On the other hand, of the 30 liver-treated cases, although 5 died,

the other 25 are still living after an average period of thirty-one months.

Factors influencing the response to liver.—The five fatal cases have already been discussed. Except in Case 30, the fatal result was due to serious complications, i.e., chronic pyelonephritis (two cases), gangrene and delusional insanity. These cases can scarcely be regarded as evidence against the efficiency of liver therapy in subacute combined degeneration. Insufficient evidence is available in the fifth case to account for the failure to respond to liver.

From a description of the unimproved cases, it will be seen that their failure to respond may be attributed to insufficient liver, cessation of the liver diet, sepsis, especially urinary or dental, or to a combination of these factors.

On the other hand, the seventeen improved cases have all had a full and prolonged course of liver treatment (except Case 6, who recovered on as little as ½ lb. a week for seventeen months). In addition, no septic complications were present.

It is thus clear that the response to liver is dependent upon the dosage of liver and the duration of treatment, the stage of the disease at which treatment is commenced, and the presence or absence of sepsis. These factors will now be considered in detail.

The dosage of liver and the duration of treatment.—The best results have been obtained by an intensive course (3½ to 4 lb. a week) for six to eight weeks, followed by 1½ to 2 lb. of liver per week indefinitely. When such large quantities cannot be taken, the equivalent in liver extract may be substituted for all or part of this amount. The extract appears to be less efficient than whole liver.

Apart from cooked liver, or liver extract, the patients have taken their ordinary diet. The modifications concerning fruit and vegetables, restriction of fats, &c., as set out in the original diet recommended by Minot and Murphy [16], have not been made.

It is interesting to note that one patient (Case 5) had not been ordered liver, but nevertheless had improved immensely. On interrogation it was found that he had been taking ¼ to ½ lb. of liver, together with ½ lb. of kidney per week for long periods as part of his ordinary diet.

As a rule the appetite returns and digestive symptoms disappear, so that the patients exhibit little difficulty in taking the large amounts of liver. In other cases, however, the patient has tired of the liver and stopped taking it, with serious results.

We find that the minimum amount of liver required to maintain the blood-count at a normal level is not as a rule the optimum required for improvement in the nervous phenomena. In others words, the amount of liver required in subacute combined degeneration is greater than that necessary in "pure" pernicious anæmia.

Stage of the disease at which treatment is commenced.—The response to liver is, as a rule, less rapid, and the amount of liver required is greater in cases where there is marked and prolonged pyramidal involvement and sphincter disturbances.

Presence or absence of sepsis.—When there is active sepsis, such as pyorrhœa or urinary infection, the improvement under liver treatment is retarded, and larger amounts are required.

Richardson [21] is inclined to connect the improvement in the nervous phenomena on liver diet with the maintenance of the red blood count at 4·5 to 5 millions. Other observers including Minot and Murphy [15] also attribute the beneficial effects chiefly to improvement in the general condition coincident with the disappearance of the anæmia.

There are several reasons why we do not agree with this view :—

(1) The spinal changes of subacute combined degeneration are not the result of a low red count, and may occur in the absence of anæmia.

(2) The red cell count may be high for long periods on moderate amounts of liver without any improvement in the nervous system.

(3) Improvement in nervous phenomena may commence when the red cell count is as low as 2 millions (see Case 9).

(4) Cessation or diminution of liver may be followed by a relapse of the anæmia without any change in the nervous symptoms and signs. (This has recently occurred in two cases in this series, Cases 16 and 24.)

It appears that the beneficial effects of liver on the nervous system is a specific phenomenon, and not the result of the maintenance of the red cell count at a high level, or of improvement in the general condition.

Etiology.

Although the cause of subacute combined degeneration is, so far as we are aware, still unknown, recently acquired knowledge has shed new light on the nature of the disease.

The improvement which occurs on dietetic measures suggests a similarity to certain deficiency diseases, such as pellagra and lathyrism, in which involvement of the white matter also occurs. In addition, it is noteworthy that the histological changes in the cord in these diseases,

bear a marked similarity to those found in subacute combined degeneration.

Bearing in mind the constancy of achlorhydria and the presence of a hereditary factor, it is possible that we are dealing with a deficiency disease occurring in persons with a certain constitutional diathesis.

In conclusion, it is evident that liver therapy has definitely beneficial effects on the symptoms and signs of subacute combined degeneration of the cord. It seems that, as with anæmia, so with the nervous phenomena, the remission brought about by liver therapy will only be maintained so long as the treatment is continued.

From clinical evidence, since all signs and symptoms of cord involvement may disappear, it would appear that the degenerative changes in the white matter in this disease are not necessarily of a permanent character.

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A STUDY OF THE HISTOPATHOLOGY OF TABES DORSALIS WITH SPECIAL REFERENCE TO RICHTER'S THEORY OF ITS PATHOGENESIS.

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Introduction.

The earliest conceptions of the histopathology of tabes dorsalis were based on the observations of Bourdon and Luys [2], who in 1861 described a sclerosis of the posterior columns and posterior roots as the result of a chronic inflammatory process, and of Charcot and Pierret [4], who ten years later described a systematic sclerosis of the posterior columns as characteristic of the disease. Pierret recognized the fact that certain parts of the posterior columns were involved in this sclerosis earlier than others, and he gave the name "bandelette externe"—or, as it is now called, "bandelette of Pierret"—to the external part of the posterior columns which appeared to be the first to degenerate. This observation was made on cases of tabes complicated by general paralysis, as it was hoped in these cases to find the early lesions of tabes. At this time Charcot and Pierret, Westphal [44], Strümpell [38], Flechsig [6], and other writers believed that the primary site of the lesion was in the spinal cord, but in 1879 Vulpian [43] suggested that a primary degeneration of the posterior columns could not lead to atrophy of the posterior roots, and he regarded the atrophy of the posterior roots as the primary lesion.

But it was not until 1894 that Obersteiner and Redlich [26], and shortly afterwards Nageotte [16], attempted to explain the lesions in the spinal cord by an inflammatory process beginning in the extramedullary posterior roots. The new theories were rapidly adopted as they seemed to explain certain symptoms commonly met with in the disease which could not be explained by a slow primary degeneration of the posterior columns of the cord. Spielmeyer [36] more recently has tried to prove, with a certain amount of success, that some degeneration uninfluenced by extramedullary processes takes place in the posterior columns. The researches of Richter [29], by introducing a new theory,

that of a specific granulomatous lesion, and those of Hassin [9], who has suggested yet another, the theory of retention of tissue fluids, have still further complicated the problem which has already aroused endless controversy: where is the initial lesion in tabes and what is its nature?

The difficulty is, of course, that cases of pure tabes do not often come to autopsy in the initial stages of the disease. If we are to ignore the cases of tabo-paresis, as Richter insists must be done, in order to eliminate possible confusion with pathological processes due to the paretic factor, then we are forced to wait, as Spielmeyer did, for chance to give us a case which does not survive the early symptoms.

If, on the other hand, we include cases of general paralysis with tabetic symptoms of recent onset, as Nageotte [17], and MacIntosh and Fildes [14] suggest, we encounter Richter's criticism [30] that we have introduced a new factor which either obscures the original tabetic lesion or makes the correct interpretation of it impossible.

But unless we are content to disregard practically all the work done on the histopathology of tabes prior to that of Richter, we must include, at least for purposes of comparison, cases of general paralysis with tabetic symptoms, for most of the early work was done on these cases. It is by no means certain how we are to assess the paretic factor. Jakob [11] particularly stressed this point. Why, he asked, should the changes found in the spinal cord and in the posterior roots in tabo-paresis be referred to the effect of the paretic process when they are not found in pure general paralysis?

In this study an attempt is made to examine three types of case: (1) Uncomplicated tabes in as early a stage as possible; (2) tabo-paresis; and (3) uncomplicated general paralysis; and to compare the observations made with a view to determining the significance of the changes found in their relation to the theories of the pathogenesis of tabes, more particularly to that of Richter.

Theories of Pathogenesis of Tabes.

The work of Pierret, to which reference has already briefly been made, demonstrated that the earliest lesion inside the spinal cord was of the middle root-fibres, the central prolongations of exogenous fibres from the posterior nerve-roots. This distinctive selection of exogenous fibres did not preclude Pierret and his contemporaries from ascribing the pathological process to a primary intramedullary degeneration of the posterior roots, though they did not attempt to explain it. When

Obersteiner and Redlich [27] brought forward their meningeal theory of the vulnerability of the posterior roots at the point where they pass through the pia mater into the spinal cord owing to the normal diminution in myelin in this position, meningeal inflammation and hypertrophy alone were held to account for damage to the roots at this "locus minoris resistentiæ," causing secondary degeneration of the exogenous fibres in the posterior colums. But that other factors besides meningitis are necessary to produce tabetic lesions was recognized by Dejerine [5], who pointed out as the best proof of this that in individuals affected with syphilitic meningo-myelitis tabes is an exceedingly rare complication.

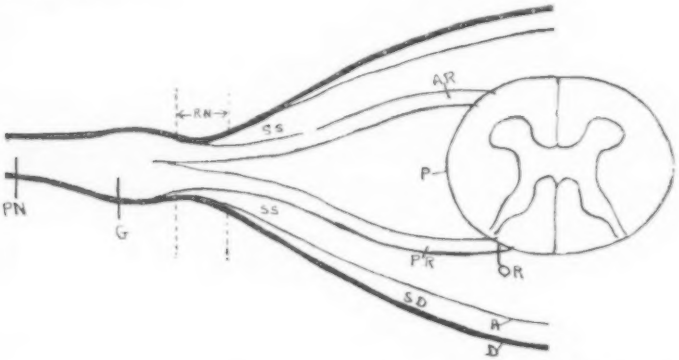

FIG. 1.—Diagram of the radicular nerve and its relations. A, arachnoidal membrane; AR, anterior nerve root; D, dura mater; G, posterior root ganglion; OR, Obersteiner-Redlich area; P, pia mater; PN, peripheral nerve; PR, posterior nerve root; RN, radicular nerve; SS, subarachnoid space; SD, subdural space. (After Richter, from Nageotte's scheme.)

The theory that syphilitic toxins acting through the medium of the cerebrospinal fluid are responsible for the lesions of tabes has received some support, though the part of the nervous system which is primarily affected has been much disputed. Orr and Rows [21] believed that syphilitic toxins could attack the nerve-fibres in any part of their course, but later [22] [23] suggested that the site of elective attack was that part of the posterior roots internal to the Obersteiner-Redlich area where they lose the sheath of Schwann. In their extramedullary course the posterior roots are protected from the effect of toxins by this sheath; on losing this they become vulnerable. Strümpell [39] and Sepp [35] placed the site of action of the toxins inside the spinal cord, but maintained that it is not the toxic cerebrospinal fluid which acts directly on

the posterior columns but a toxic exudate from the meninges. The toxic agency of the meningitis was also held responsible for the tabetic lesions by Bresowsky [3], but he placed the lesion at the Obersteiner-Redlich area and not in the spinal cord itself. Alford [1], by the injection of iron salts into the subarachnoid space and subsequent fixation with hydrochloric acid, demonstrated that iron granules were carried into the spinal cord along the posterior roots for some distance, particularly in the lumbar region, and that no granules were carried along the anterior roots. He therefore concluded that syphilitic toxins in the meningeal spaces travel along the posterior roots in the same way, and that the initial lesion consists in a degeneration of the entering root fibres just inside the Obersteiner-Redlich area, where the toxins come into contact with them.

Spielmeyer has been the chief protagonist of recent years of the endogenous, "primary degeneration" theory, but in one paper [37] he has made statements which appear to be contradictory. After quoting his observations that degeneration of the posterior roots takes place almost entirely within the spinal cord, he agrees with Obersteiner and Redlich that the process begins just inside the pia mater where there is a natural constriction of the roots, but he then proceeds to consider the degeneration of the central prolongations of the posterior roots in the posterior columns as a "systemic independent disease process," and says definitely that "there is no evidence that this follows changes at the Obersteiner-Redlich area." It is difficult to reconcile the two statements. In another communication [36] Spielmeyer quotes a case which, in view of the short history and the detailed histological examination, is of importance from the point of view of the earliest lesions, and will therefore be briefly summarized :—

The case was that of a man who died at the age of 56, after having had typical tabetic symptoms and signs for nine months only. Four weeks before death mental symptoms appeared. Histologically, in the spinal cord from the level of the first sacral segment to the first lumbar there was seen typical degeneration of the posterior columns. Above this level the degeneration corresponded to the roots from these regions. With Scharlach R. stain much degenerating myelin was stained in the root entry zone and in the area corresponding to the continuation of these fibres into the posterior columns. In the root regions the first sacral and lowest lumbar segments were the most affected. Degeneration did not extend into the root bundles, but ceased at the place where the roots take on their peripheral character, i.e., at the Obersteiner-Redlich area. Spielmeyer could find no degeneration peripheral to this. Meningeal changes were few, and consisted solely in slight infiltration of the

pia-arachnoid, mainly in the cervical region, with small lymphocytes. The only change seen in the nerve roots was a slight infiltration under the dura with lymphocytes, and this only in a few nerve roots. Spielmeyer felt justified in concluding from this case that the essential pathological process in tabes consists in an independent degeneration of the intramedullary posterior roots, which stops short at the place where they take on a peripheral character, i.e., the Obersteiner-Redlich area, the boundary between neuroglial and connective tissue.

Richter [31] attempted to show that the discrepancy between the degeneration in the intra- and extra-medullary roots observed by Spielmeyer was apparent rather than real by conducting experiments on cats. He sectioned the extramedullary posterior roots to determine whether this injury would cause the intra- and extra-medullary roots to degenerate at the same rate. Eighteen days after section of the extramedullary roots myelin degeneration in them had reached the lipoid stage, whilst in the intramedullary roots only the Marchi stage had been reached. Therefore, at the time when lipoid material would stain in the intramedullary roots, it would have disappeared from the extramedullary roots. Richter also pointed out that as one root alone may be affected by the tabetic process for months or even for years, it is possible at an advanced stage in the disease to find in adjacent roots the early phase of the breaking up of myelin and more advanced lipoid changes. The validity of Richter's objection to Spielmeyer's conclusions from this early case rests on the answer to the question how far experimental section of roots can be considered analogous to the slow process which causes degeneration of the roots in tabes.

The theory which found most general acceptance until Richter propounded his "specific granuloma" theory was that of Nageotte [16]. The case on which he founded his localization of the primary lesion was one of dementia paralytica, with very slight posterior column degeneration. Nageotte came to the conclusion that the primary lesion was limited to that part of the posterior root which lies between the point where it leaves the subarachnoid space to join with the anterior root and the spinal ganglion. This part of the posterior root Nageotte called the "radicular nerve." The nature of the lesion he considered to be an interstitial "radiculitis," by which he meant an infiltration with lymphocytes, plasma cells, and what appeared to him to be embryonic cells, with fibrosis of the interstitial tissue of the nerve limited to the area of the posterior root. The degeneration of the posterior root he took to be a secondary phenomenon due to pressure from the infiltrating tissue. Nageotte explained the escape of the anterior roots in this

situation by supposing either that they were less susceptible to this particular form of trauma, or that they were capable of regeneration. His own definition [18] of the pathological entity of tabes summarizes very well his view of its pathogenesis: "Tabes is characterized anatomically by an inflammatory lesion which attacks a certain number of sensory or motor roots at their exit from the subarachnoid space and which is dependent upon generalized syphilis of the meninges." He was insistent [19] that meningitis, although invariably present, does not itself cause tabes except through the intermediary of the radiculitis, and that this affection of the radicular nerve is the sole criterion of the tabetic process. Thomas and Hauser [41] confirmed Nageotte's findings of inflammatory changes in the radicular nerve. They also found a constant meningitis in each of their eleven cases, which was sometimes more extensive over the anterior roots than over the posterior. Similar observations were made by Schroeder [34], and by Bresowsky, who found infiltration of the pia-arachnoid in every one of the forty cases he examined.

Jakob [12], Hassin [7] [8], and Schaller [33] have also reported constant inflammatory changes in the meninges. The opinions of two of these writers on the relationship of these findings to the pathogenesis of tabes will be dealt with later in discussing their attitude to the Richter theory.

This theory, formulated by Richter in an exhaustive study, has been accepted up to the present time as the one which best explains the clinical course of the disease. Richter holds the view that the primary and essential lesion in tabes is the settling down of spirochætes from the cerebro-spinal fluid in elective parts of the cerebro-spinal axis. These sites of election are the radicular nerves. The spirochæte then acts as a "formative irritant," and a specific granulation tissue is formed which has its origin in the lymph spaces of that part of the common sheath which lies nearest to the ganglion. This granulation tissue spreads into the perifascicular spaces and the radicular nerve is eventually enclosed by this mass of newly-formed tissue. In late stages of the disease the granulation tissue undergoes regressive changes and becomes sclerosed, thus pressing upon the nerve-fibres and destroying them. Richter's own description [29] of the lesion is: "The granulation growth in the lymph and tissue spaces is the initial, primary and autonomous change in tabes. The extension of the process to the root-nerve causes a secondary root affection."

No lymphatics have hitherto been described in the radicular nerve

or in the meninges; neither have spirochætes yet been demonstrated in the cerebro-spinal fluid of tabetics. But apart from these hypothetical considerations the question of the specificity of this "granulation tissue" has to be investigated. Richter described the cells of which it consisted as endothelial in type, but capable in the later stages of the disease of forming fibroblasts. As Hassin [9] has recently pointed out, these cells bear a very strong resemblance to the arachnoidal cells, and they are by no means "specific" for tabetic nerve-roots. Hassin observed them around the periphery of several normal nerve-roots, and it is hoped to show in this study that they are constantly present in considerable numbers in nerve-roots throughout the spinal axis and that they may even be perifascicular.

Richter [30] strenuously denies the presence of any inflammatory changes in the radicular nerve in cases of pure tabes. These occur, he says, only in cases of tabo-paresis and are then due entirely to the paretic factor. Hassin agrees with Richter that hæmatogenous elements play no part in the lesion of the radicular nerve. Jakob, on the other hand, found plasma cells and lymphocytes infiltrating the radicular nerve in cases of pure tabes, though he is inclined to the opinion that these may be histogenous rather than hæmatogenous. The question of a difference in intensity between the affection of the roots in their intra- and extra-medullary course, that is, at their point of entry through the pia mater at the Obersteiner-Redlich area, is summarily dismissed by Richter as he does not believe that this difference has been proved.

Meningitis is, according to Richter, a common syphilitic accompaniment of tabes but not a constant change, and it consists in an inflammatory lesion of the pia-arachnoid entirely independent of the tabetic process, and also independent of the posterior column degeneration. The frequency with which meningitis occurs in tabes depends on both lesions being caused by the presence of the spirochætes in the sub-arachnoid space, but in tabes the spirochæte settles in the root-nerve and in meningitis in the pia mater. The difference in reaction is due to the anatomical peculiarities of the two sites.

The posterior column degeneration is considered by Richter to be secondary to the lesion in the radicular nerve. In his twenty-four cases he could find "no indication which would allow him to accept any independent degeneration in the spinal cord."

He stresses, as additional evidence to his experimental work, the not uncommon cases in which the posterior column degeneration is asymmetrical, and remarks that in most cases a true asymmetry unrevealed

by coarse staining methods really exists between the degeneration on the two sides which is probably due to variability in the numbers of spirochætes settling in the corresponding roots and therefore to differences in the intensity of the granulation process.

Changes in the posterior root ganglia Richter also considers secondary to the lesion of the radicular nerve as they are analogous to those found by Köster [13] after experimental section of the posterior roots. Excess of lipochrome pigment, shrinkage of the ganglion cells and hyperplasia of the capsular nuclei were the changes most often observed. Chromatolysis occurred only very rarely. The resistance of individual ganglion cells plays a large part in determining the extent of the lesion, as some ganglia from a certain case may be severely damaged whilst others appear normal. No inflammatory changes were seen in cases of pure tabes, but in the cases of tabo-paresis both perivascular and diffuse infiltrations with lymphocytes and plasma cells were found extending into the ganglia from the corresponding root-nerves.

Richter [29] also investigated the changes in the cranial nerves. It is not proposed to deal here with his findings in any detail, but briefly, he described amongst the extracerebral fibres of the third and fifth nerves a granulation tissue identical with that which he observed in the radicular nerves. In the optic nerves of cases with optic atrophy no granulation tissue was seen, but there was a vascular reaction characterized by infiltration with plasma cells and lymphocytes. This difference in reaction Richter explains by the fact that the optic nerve is developmentally of central origin and therefore reacts to noxious stimuli in the same manner as the central nervous system.

But the support that was given to Richter's theory was due not to his description of a "specific" tissue, but to the fact that he had been able to demonstrate spirochætes in this tissue in three cases out of nine of pure tabes and in one case out of four of tabes with spinal syphilis.

Most of the criticism that has been directed against Richter's theory has come from Jakob [11], from Wohlwill [45], and from Spielmeyer [36]. The latter could not convince himself that Richter's findings were at all constant. His views have already been given.

Jacob emphasizes the constant spinal meningitis observed by him and also by Hassin in the material studied by him in Jakob's laboratory. He points out that whilst Hassin regards the changes in Nageotte's area as the most important, Richter looks upon the specific lesion in this region as the only one of importance.

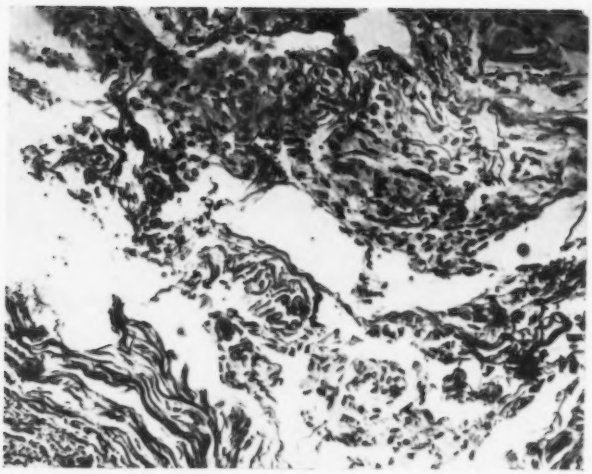

FIG. 2.—Section through the radicular nerve of a case of uncomplicated tabes, stained with hæmatoxylin and counterstained with van Gieson. Two arachnoidal tufts are present and extend between the nerve-fibres.

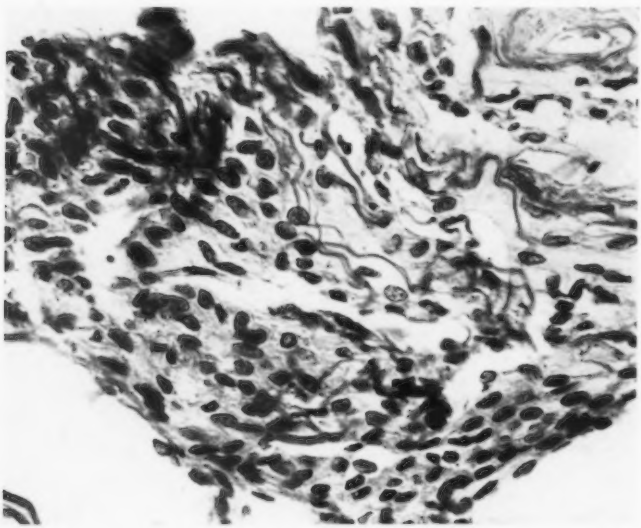

FIG. 3.—A portion of the same section as fig. 1, under higher magnification to show the endothelial character of the infiltrating arachnoidal cells.

To illustrate paper by R. O. Stern.

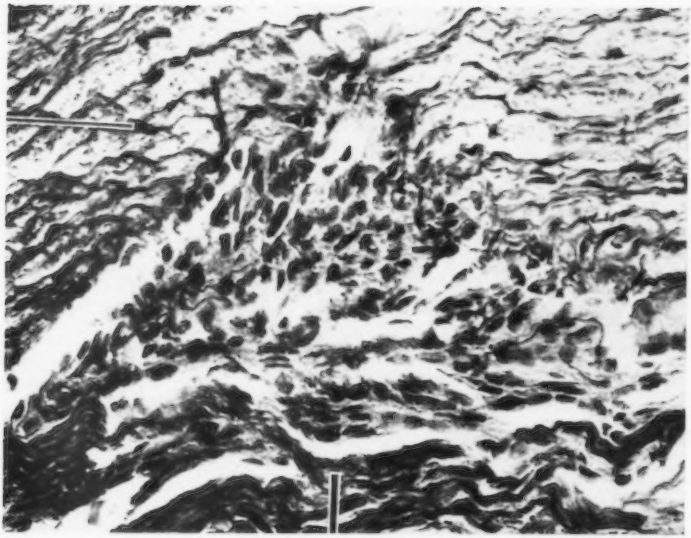

FIG. 4.—Section through the radicular nerve of a case of subacute combined degeneration of the cord stained with hæmatoxylin and counterstained with van Gieson. An arachnoidal tuft can be seen infiltrating the nerve-fibres. Isolated arachnoidal cells are also present and lie between nerve-fibres.

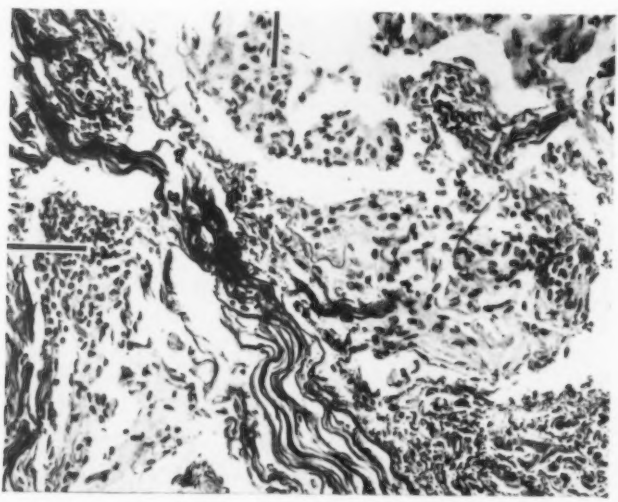

FIG. 5.—Section through the radicular nerve of a case of uncomplicated tabes stained with hæmatoxylin and counterstained with van Gieson. Several arachnoidal tufts are present, and in addition there is much infiltration with small lymphocytes.

To illustrate paper by R. O. Stern.

Jakob is of the opinion that although the granulation tissue described by Richter undoubtedly occurs in Nageotte's area, its distribution is not limited to this area but extends to the arachnoid covering the spinal cord. He found infiltrations with lymphocytes and plasma cells as well as granulation tissue in the Obersteiner-Redlich area in cases of pure tabes, and is convinced that damage to the nerve-fibres in this region is an important contributory factor in causing degeneration of the intramedullary posterior roots.

Wohlwill criticizes Richter for his interpretation of his histological findings as a new growth of granulation tissue which actually destroys the nerve-fibres by invasion and ultimate strangulation. The process as conceived by Richter resembles, according to Wohlwill, that seen in infiltration by a malignant neoplasm rather than pressure from sclerosing granulation tissue. Richter does not mention other possible ways in which this tissue could injure the nerve-fibres, as, for example, by the blocking up of lymph channels or other nutritional disturbances. Wohlwill also draws attention to the fact that the case which Richter describes as one of "incipient tabes" had had symptoms for three years, and can therefore not be accurately described as representing the earliest stages of the disease process.

Hassin has recently published a paper in which he presents a modification of Richter's hypothesis on the effect of the granulation tissue in the radicular nerve on the tabetic process. Hassin does not consider that the cells composing the "granulation tissue" in Nageotte's area are specific formations caused by the presence of the spirochæte in the cerebrospinal fluid, but that they are arachnoidal cells which have proliferated in response to irritation from an inflamed dura mater, which is a lesion constant in tabes. These cellular masses obstruct the perineural spaces by invading them and interfere with the escape of cerebrospinal fluid from the subarachnoid space. Stasis of the cerebrospinal fluid therefore occurs, and as, according to Hassin, drainage of the tissue fluids from the posterior columns is performed chiefly through the perineural spaces of the posterior roots, this part of the spinal cord is the first to undergo degeneration. Hassin cannot accept the mechanical "strangulation" theory of Richter, as the invading arachnoidal cells are rarely found between the fasciculi in the radicular nerve; they are usually confined to the margins of the fasciculi. Moreover, they are practically never seen in relation to the nerve-fibres.

But Hassin, after having advanced his modification of Richter's theory and having described the degeneration of the posterior columns

of the spinal cord as a secondary phenomenon due to a "tissue fluid stasis" caused by blocking of the perineural spaces, goes on to state that the degeneration of the posterior columns must be considered a primary process which originates within the spinal cord itself. This degeneration was seen in the form of an "island-like" degeneration, which Hassin considers typical of tabes, the islands consisting of demyelinated areas in which the nervous elements are mainly replaced by neuroglial tissue, although thin axons are usually preserved.

But if Hassin's theory is correct and the degeneration of the posterior columns is caused by retention of tissue fluids we should expect to find the amount of degeneration in the posterior columns to correspond more or less exactly to the intensity of the arachnoidal infiltrations.

Other lesions observed by Hassin agree with those already described by many other writers. But in the spinal ganglia he found evidence of satellitosis and neuronophagia in addition to shrinkage of cells and excessive accumulation of pigment in the ganglion cells.

Spirochætes in Tabetic Lesions.

The only positive spirochæte findings recorded in tabes previous to Richter's were those of Noguchi [20], who found one or two spirochætes in the posterior columns of a case of tabes complicated by meningo-myelitis, and of Versé [42], who claimed to have found them in two cases: in one in the spinal ganglia, lying in the ganglion cells and also between them, in the other in the nerve roots. Richter rather doubted Versé's results on the ground that impregnated nerve-fibres closely resemble spirochætes. Richter used Noguchi's method and mentions that Jahnel's method was unsuccessful even in those cases which were positive by Noguchi's method. This is surprising as Jahnel's method has been found to give consistently good results in this country. Richter found only very few spirochætes in his positive cases, and of these, relatively morphologically intact forms were very rare. Most of them were degenerated forms and little heaps of "degenerated spirochæte fragments" were seen. The spirochætes were found only in the "granulation tissue" with one solitary exception, which was found in the thickened covering of a root bundle. Richter contends from many negative findings that there are tabetic root nerves in which no spirochætes occur.

There is no reason for supposing that spirochætes were not present in the tissue which Richter described, especially as one of his

sections was confirmed by Jahnel, but it is possible if the "granulation tissue" is composed of arachnoidal cells that spirochætes have been "swept in" to the perifascicular spaces together with these cells, and that they are to be considered as a fortuitous finding. Jahnel [10] found spirochætes in the subarachnoid spaces of one case which he examined with the dura mater intact. It is possible that in this case the spirochætes were really present in the subdural space, and that this is their usual habitat in tabes. This would explain the negative findings of many observers, as the dura is but rarely included in sections of the spinal cord.

It is here convenient to summarize those theories of the pathogenesis of tabes which have been considered:—

(1) A primary degeneration of the intramedullary posterior roots. (Charcot and Pierret, Westphal, Strümpell, Flechsig, Sepp, Spielmeyer.)

(2) Meningeal inflammation causing direct pressure on the posterior roots at their passage through the pia mater. (Obersteiner and Redlich.)

(3) Influence of syphilitic toxins on the posterior roots. (Orr and Rows, Marie and Guillain [15], Bresowsky, Alford.)

(4) Inflammatory changes in the radicular nerve. (Nageotte, Thomas and Hauser.)

(5) Granulomatous formation in the radicular nerve. (Richter.)

(6) Retention of tissue fluids in the spinal cord, due to obstruction by proliferating arachnoidal cells. (Hassin.)

Certain writers, notably Jakob and Schaffer [40] (in his article in Lewandowsky's "Handbuch der Neurologie"), do not consider that any one theory will explain all the clinical phenomena, and they therefore regard the pathological process in tabes as consisting of a combination of two or more of the processes enumerated above. The conclusions arrived at from the results of this study will be given later.

Report on Pathological Material investigated.

The material at my disposal was derived from nine cases of pure tabes, three cases of tabo-paresis and eight cases of general paralysis. In addition, the posterior root ganglia from twenty-seven cases taken at random from the post-mortem material available, which included examples of most of the common diseases of the spinal nervous system and three cases in which the spinal cord and its meninges could definitely be said to be normal, were examined as controls. The Gasserian ganglia complete with dural sheaths from two normal cases were also examined.

The duration of symptoms in the tabetic cases varied from twenty

months to twenty-one years. In two cases of pure tabes no clinical history was available, but the cases were obviously of long standing from the amount of sclerosis present in the ganglia and roots. In two cases of taboparesis the cerebral and spinal symptoms appear to have developed at the same time, the total duration of symptoms being twelve months in one case and six months in the other. In the third case the history was that of a "nervous breakdown" eighteen months previously, but only three months prior to admission had there been symptoms of a spinal lesion. This case already exhibited the typical tabetic signs of Argyll Robertson pupils, partial analgesia to pinprick over the chest, ataxia and inco-ordination of both legs with absent knee and ankle jerks, and it seemed probable, in view of the very short history, that here was a case which should show the earliest tabetic lesions.

Sections of the posterior root ganglia were made longitudinally to include the radicular nerve and posterior-root and, wherever possible, ganglia from the cervical, dorsal and lumbar regions were examined. Similar regions of the spinal cords were sectioned, with their meninges and roots attached.

Microscopical Examination.

The staining methods employed were those of hæmatoxylin with van Gieson's counterstain for the ganglia and posterior roots, Scharlach R., hæmatoxylin with van Gieson, Kultschitsky-Pal and (in the more recent cases) Bielschowsky, for the spinal cord.

Sections from all the syphilitic posterior root ganglia and from the spinal cords of the pure tabes cases were stained by Jahnel's method for spirochætes.

As the main purpose of this study was to investigate the changes in the radicular nerve from the point of view of the Richter hypothesis, the lesions detected in them will be considered first. Except where differences existed between the lesions in the cases of pure tabes, taboparesis and general paralysis, the descriptions given below cover the three types of case.

(1) *Infiltrative lesions.*—Epidural infiltration with lymphocytes and plasma cells was common, but was present to the greatest extent in the cases of general paralysis and tabo-paresis. It may be stated here that in the cases of general paralysis and tabo-paresis plasma cells were more commonly observed in hæmatogenous infiltrations than they were in cases of pure tabes. The infiltrating cells were frequently found in small clusters or heaps, as well as lying scattered throughout the epidural space.

Subdural infiltrations with lymphocytes and plasma cells, although less generally seen in the cases of pure tabes, certainly occurred in the majority of cases, particularly in relation to the blood-vessels. In the cases of general paralysis and tabo-paresis these infiltrations were constant and, in a few cases, particularly those of tabo-paresis, the focal arrangement of the infiltrating cells was striking. The cells did not in most cases penetrate between the nerve-fibres, but occasionally some could be seen separating the nerve elements. More often the cells were limited to the periphery of the nerve-bundles.

(2) *Vascular changes.*—The walls of the blood-vessels in the radicular nerve were much thickened in cases of pure tabes of any standing, and in all cases there appeared to be at first sight a great excess of that peculiar degeneration of blood-vessels which gives rise to "corpora arenacea" or psammoma bodies. But on comparing the numbers of these bodies in normal radicular nerves with those in the tabetic nerves it was found that normal nerves contained as many, if not more, of these bodies than did the tabetic ones.

It is necessary to point out that the age of the arteries plays no part in the development of these bodies, as they were found in considerable numbers in the nerves of a boy aged 19. The mode of production of these bodies from blood-vessels is quite unknown. They are mentioned here only to demonstrate that their presence in large numbers in the radicular nerves in tabes has no connection whatsoever with the tabetic process.

(3) *Fibrosis of meninges.*—The dura mater covering the radicular nerves and ganglia was thickened in every case examined, but the thickening was greatest in the most long standing cases of pure tabes. The perineural sheaths of the radicular nerves were slightly thickened in all cases of pure tabes, but a true fibrosis affecting the nervous elements by pressure was seen only in one case, that of twenty years' duration.

(4) *Richter's specific "granulation tissue."*—In considering the "granulation tissue" which Richter described, it must be noted that Hassin has already recognized the cells of which this tissue is composed in the radicular nerves of non-syphilitic cases. Some years before the appearance of Hassin's paper Dr. Greenfield and Dr. Wolfsohn observed these cells during their investigation, in this laboratory, of the radicular nerves in a case of the Charcot-Marie-Tooth type of muscular atrophy, but they did not publish their observation. They have kindly given me the opportunity of examining sections of the radicular nerves from this

case, and in addition sections have been taken from the following cases (the age of the patient is given in parenthesis after the disease).

Four cases of disseminated sclerosis (51, 46, 43, 30).

Four cases of subacute combined degeneration of the cord (63, 60, 54, 49).

Three cases of secondary carcinoma involving the spine (60, 53, 40).

Two cases of disseminated myelitis (37, 32).

Two cases of sarcoma of the spine (63, 29).

Five cases of syphilitic myelitis (53, 46, 44, 30, 27).

One case each of peripheral neuritis (48), tuberculosis of the spine (51), chloroma (19), cerebral hæmorrhage (74), cerebral thrombosis (69), cerebral abscess (50), and fracture of the spine (50). Also, the Gasserian ganglia were examined from two cases; one a case of cerebello-pontine angle tumour (25), the other a cerebral abscess (29).

My observations agree with those of Greenfield, Wolfsohn and Hassin. There is no evidence that the cells of which this "granulation tissue" is composed are newly formed, and it is quite clear that their existence does not necessarily depend on the presence of the spirochæte since they were present in twenty-two out of the twenty-seven control cases. They differ in no wise in histological appearance from the simple arachnoidal cells of the arachnoid membrane. These are characterized by having oval nuclei with a very distinct nuclear membrane, inside which the chromatin is arranged in a stippled or dotted manner; they are in fact characteristic endothelial cells. The suggestion of Richter that these cells can and do become transformed into fibroblasts in the late stages of tabes is not confirmed by my observations. The appearance of the cells in a case of three months' duration (tabo-paresis), or in a case of pure tabes of twenty months' duration, is identical with that in cases of pure tabes of five, ten, or even twenty years' duration. If it were possible that these cells could undergo metamorphosis, some intermediate stage between an endothelial type of cell and a fibroblastic type would be seen in material from cases which varied so much in duration.

Hassin rightly contended that these cells very rarely penetrate between nerve-fibres; they are almost invariably confined to the periphery of the nerve bundles. He believes, however, that not only is the actual number of arachnoidal cells in the radicular nerve increased in tabes, but that in this condition they occur in the radicular nerves at all levels of the spinal cord, whilst in normal cases the cells are seen only at one level—at which level and why is not stated.

In this study radicular nerves from the cervical, dorsal and lumbar regions of twenty-seven control cases were examined and arachnoidal cells were found at all these levels, although they were not found at every level in every case. Furthermore, they may infiltrate the nerve-bundles in non-tabetic cases, and even appear between the nerve-fibres. Such an appearance is illustrated in fig. 3 from a case of subacute combined degeneration of the spinal cord. Their numbers in non-syphilitic cases may equal and even exceed those in tabetic cases. Only those cases of tabes with much generalized arachnoiditis showed an excessive number of arachnoidal cells in the radicular nerve. It is probable that in these cases the prolongations of arachnoidal membrane into the radicular nerve share in the general proliferation of arachnoidal cells.

It is clear therefore, in the first place, as Hassin has already pointed out, that the cells of Richter's "granulation tissue" are not specific for tabes, and in the second place, as they may occur in normal radicular nerves in like number and with the same distribution as in tabes, they can have no essential connection with the pathological process of this disease.

Reference has already been made to the integrity of the nervous elements in the radicular nerve except in cases of long standing. This is in accordance with the findings of Hassin. Although Richter described destruction by pressure of the nerve-fibres in this region it must be remembered that the duration of symptoms in his least advanced case was three years.

Changes in the Spinal Ganglia.

In several cases of general paralysis and of tabo-paresis there were definite inflammatory changes in the spinal ganglia with infiltration with lymphocytes and plasma cells, but in only one case of pure tabes were there inflammatory changes. There was much fibrosis of the spinal ganglia in three long-standing cases of pure tabes. The most noteworthy lesions found in all the ganglia were hypertrophy of the capsule cells of the ganglia and an increase in the pigment content of the ganglion cells. In many cases the ganglion cells appeared to be shrunken, but as much of the material had been preserved for some years, and the majority of the preparations of the ganglia had been embedded in paraffin, it is difficult to decide how much of this shrinkage was due to artefact and how much to cellular change. As Orr and Rows pointed out many years ago, most of the changes described in ganglion cells are the result of artefact or bad fixation. Certainly no

confirmatory evidence of degeneration of these cells, as chromatolysis or neuronophagia, could be detected in my series.

The Spinal Meninges.

The spinal meninges were thickened in all cases of pure tabes, the pia being especially affected. The thickening was not more evident in the area of the entry of the posterior root than in that of the anterior root. There was no variability in the degree of thickening in the several regions of the spinal cord. In one case changes in the meninges had to be disregarded in relation to the tabetic process, as a septic meningitis had occurred following operation for relief of tabetic crises. Of the other eight cases four exhibited considerable cellular infiltration of the pia with small lymphocytes and a few plasma cells, whilst in the other four cases lymphocytic infiltration was very slight, though not completely absent. In no case could it be observed that the infiltration of the pia was confined to, or greater in, the region of the posterior roots. In long-standing cases the vessels of the pia were thickened and perivascular infiltration with lymphocytes was not uncommonly found. In the cases of paralysis and tabo-paresis inflammatory phenomena in the meninges were much more intense, although thickening of the meninges was not so great as in the pure tabes cases. Plasma cells were very numerous and perivascular infiltration with lymphocytes was not uncommonly found. No difference in degree of infiltration between the posterior and anterior root regions could be determined.

The Spinal Cord.

In describing the lesions in the spinal cord it is convenient to take the three types of case separately. Kultschitsky-Pal preparations of the spinal cord in the pure tabes cases revealed the characteristic picture of posterior column demyelination with the incidence greatest on those nerve-fibres which represent the lumbar roots, and which in the lumbar region are confined to the postero-external part of the posterior columns, in the "bandelette of Pierret." Why these fibres should be the first to degenerate is unknown. Richter's theory that the lumbar roots are first affected because they run vertically and the spirochætes sink by the force of gravity into their meningeal coverings and there cause the specific reaction, cannot be entertained seriously.

The rate of degeneration of the fibres varies within wide limits.

It was surprising to find that in a case with a history of five and a half years' duration which was characterized by the occurrence of violent

gastric crises with very few symptoms of ataxia or inco-ordination, but with typical signs (e.g., Argyll-Robertson pupils, breast plate analgesia, absent ankle-jerks), practically no posterior column degeneration could be made out in any region of the spinal cord. The only lesion appeared to be the loss of a few myelinated fibres in the root entry zone of the mid-dorsal region. In this case there were considerable inflammatory changes in the radicular nerves.

By way of contrast, in the case of pure tabes with the shortest history—of twenty months only—most extensive posterior column degeneration was present.

The cases of tabo-paresis were most instructive from the point of view of posterior root degeneration. In the case with a history of spinal symptoms of only three months' duration, very little demyelination was expected in the posterior columns. Advanced myelin degeneration was found, however, in the lumbo-sacral region and could be traced upwards in the cord to a corresponding degeneration of most of the column of Goll in the cervical region. The degeneration had already reached the lipoid stage and was well seen in Scharlach R. preparations. Droplets of fat could be traced outwards to the most external part of the root entry zone, but they did not extend into the extramedullary portion of the roots, in which the myelin was normal.

In this case most of the degenerative products of myelin were in the same stage, therefore degeneration of the posterior roots must in some cases at any rate occur very rapidly, as it did in this case. Degeneration of these roots is therefore not always due to a slow strangulation such as Richter suggests.

In another case of tabo-paresis with a history of six months' duration, no posterior column degeneration could be determined. It was impossible to determine which factor differed in the two cases. Meningeal infiltration, inflammatory changes in the radicular nerves, arachnoidal proliferation, did not seem to vary to any extent in the two cases.

In the third case of tabo-paresis, although no lipoid substances could be stained by the Scharlach R. method, Kultschitsky-Pal preparations showed that myelin degeneration was present in the posterior columns of the lumbar region. At the end of twelve months therefore a stage had been reached in which lipoid substances had already been removed—further evidence of the rapidity with which degeneration can in some cases take place in the intramedullary roots. The cases of uncomplicated general paralysis were also examined by fat-staining methods to

determine whether any posterior root degeneration was present. None could be detected. Jakob's opinion that it is permissible to include cases of tabo-paresis with spinal symptoms amongst cases for the investigation of early tabetic lesions is therefore confirmed. Lesions which occur in parts of the nervous system which are not affected by pure general paralysis should not be ascribed to the paretic process.

Result of Examination for Spirochætes.

The examination of the radicular nerves, spinal ganglia and spinal cords for spirochætes must be reported negative, for although in one case of pure tabes a single spirochæte-like body was seen in the posterior column of the cord, it was not typical and no others could be found in other sections from the same case. It is not justifiable therefore to regard this as a positive finding. Many structures which stained deeply with silver were encountered in the ganglia and radicular nerves. These might have been degenerating spirochætes or products of their degeneration. They were certainly neither nerve-fibres nor deposits of silver, but because not one typical form could be seen these structures were rejected as positive results.

DISCUSSION.

The results of this study have in the main been more destructive than constructive. Evidence has been brought forward that the theory of pathogenesis propounded by Richter does not bear the test of investigation. In the first place the cells of which his "specific granulation tissue" is composed are not specific for tabes, as Hassin first pointed out (although he was not the first to make the observation); they are arachnoidal cells and they may occur with the same distribution and in equal numbers in the radicular nerves of normal cases. These cells were seen in this situation in twenty-two out of twenty-seven control cases, and in two controls they were found around the periphery of the nerve-bundles of the fifth nerve as it enters the Gasserian ganglion. Secondly, the degeneration which occurs in the intramedullary part of the posterior root may be present as early as three months after the onset of symptoms, whilst eighteen months after the onset of symptoms suitable staining methods may demonstrate the presence of a lesion of the myelin sheaths in the posterior columns of long standing. On account of the rapidity of the degeneration in the intramedullary roots in certain cases, therefore, Richter's theory of a slow strangulation of the posterior roots by this "granulation tissue" is untenable.

The theory of Hassin is subject to criticism from several points of view. But the whole theory is founded on a fallacy because in normal cases with similar arachnoidal infiltrations there is no degeneration of the posterior columns. Further, in tabetic cases there is no correspondence between the intensity of the arachnoidal infiltrations in the radicular nerves and the amount of posterior column degeneration.

The whole problem of the site and nature of the primary lesion in tabes turns upon the point that we do not know for certain where it is the spirochæte first settles in the nervous tissues. In spite of many attempts to find the spirochæte in tabetic lesions, only four observers have been successful. Noguchi found a few in the posterior columns of one case. Versé described them in the spinal ganglia and posterior roots of two cases. Jahnel [10] discovered a very few in the meninges of one case when he examined the spinal cord with the dura mater intact. Richter has described them (and one of his sections was confirmed by Jahnel) in the arachnoidal proliferations. They have never been described as occurring in the subdural space, though they may possibly exist in this situation as Jahnel was only able to find them in a case in which the dura was intact.

But it may not be necessary for spirochætes to be present constantly in the central nervous system in order to produce tabetic lesions. Orr and Rows [24] [25] showed clearly that bacterial toxins will pass along the afferent nerves by the perineural lymph-stream without causing any changes in the peripheral nerves and will produce degeneration of the posterior columns of the spinal cord indistinguishable from that of tabes. They introduced capsules containing different bacteria in contact with the afferent nerves of animals and produced posterior column degeneration. They also observed a similar degeneration in the spinal cords of patients who died following peripheral septic lesions, e.g., boils, superficial abscesses. If we accept the possibility that a tabetic degeneration may also be caused by the toxins from spirochætes which exist outside the central nervous system, then it is necessary to find a focus in which the spirochætes may live for many years whilst pouring out their toxins along the afferent nerves. It is well known that certain parts of the body offer a suitable nidus for harbouring spirochætes for many years. The aorta is the chief of these. MacIntosh and Fildes [14] did not correlate aortitis with tabes, but they pointed out that in many cases examined at random post mortem a syphilitic aortitis was the only demonstrable syphilitic lesion, and that the aorta was a possible source of spirochætes which might wander out into other tissues of the body

at intervals and cause various syphilitic manifestations. Spirochætes have not been found in the aorta in tabes, but Jahnel has found them there in general paralysis. In my study attempts were made to find them in the aortas available in two cases of tabo-paresis (in one of which spirochætes were present in the cerebral cortex), in one case of pure tabes, and in one of general paralysis, but without success. Further work on this aspect of the subject is necessary.

Summary and Conclusions.

(1) A review of the most important theories of the pathogenesis of tabes has been given.

(2) A series of cases of uncomplicated tabes, of tabo-paresis and of general paralysis has been studied with special reference to the lesions in the radicular nerves and the Richter theory of pathogenesis. In addition a series of twenty-seven control cases has been studied for comparison.

(2) Evidence has been brought forward to prove that neither Richter's theory nor Hassin's modifications of it is capable of explaining the pathogenesis of tabes.

(4) Reference is made to the work of Orr and Rows on degeneration of the posterior columns caused by bacterial toxins from peripheral foci and the bearing this work has on the pathogenesis of tabes. The suggestion is made that in tabes the aorta may act as a focus from which spirochætes may exert their toxic effects on the central nervous system.

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DIPLOPIA WITHOUT EXTRA-OCULAR PALSIES, CAUSED BY HETERONYMOUS DEFECTS IN THE VISUAL FIELDS ASSOCIATED WITH DEFECTIVE MACULAR VISION.

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DURING the course of a recent study of tumours of the hypophysis, of the hypophyseal stalk, and of the suprasellar meninges (Beckmann and Kubie [1]), it became apparent that among the visual symptoms diplopia occurred with surprising frequency. Sometimes the diplopia was explicable by the existence of palsies of the extra-ocular muscles. In a certain number of cases, however, there was neither history nor physical sign of strabismus, ptosis, or pupillary disturbances. Furthermore, where the record furnished sufficient data it was evident that the diplopia was most troublesome when the patient attempted to fix both eyes on an object for precise observation, and that it was not influenced by conjugate deviation of the eyes in any direction (whereas diplopia which results from weakness of any of the muscles of the eye is always altered in some way by conjugate deviation of the eyes).

This type of diplopia had not occurred in any patients with homonymous defects in the visual fields, but only in the presence of bitemporal hemianopia. Theoretically, it could occur in the presence of binasal hemianopia as well, but no examples of this type of field defect occurred among the cases studied. Not all patients with bitemporal hemianopia developed diplopia, however; and a review of the histories made it clear that diplopia occurred only in association with periods of amblyopia. Where the amblyopia was transient, the diplopia was transient; where the amblyopia was permanent, the diplopia persisted.

In one case (Case 1), it was our good fortune to watch the development of the double vision, and to see that it occurred when the bitemporal

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defects in the visual fields had actually invaded the macula. In the other cases presented below, it is possible to deduce a similar progression of the lesion from the data in the histories and in the examinations.

The conditions necessary for the development of this type of diplopia would seem to be these: (1) heteronymous defects in the visual fields (bitemporal or perhaps binasal); (2) reduction of visual acuity at the maculæ to less than that of the adjacent areas on the relatively normal halves of the retinæ; (3) the power to project the image perceived into space accurately in relation to the point of the retina on which the image falls (i.e., normal central-retinal localization).

Under these conditions the patient attempts to improve his binocular vision by using perimacular fields. If, in so doing, he uses homologous fields, one image will fall upon the amaurotic half of one retina, and he will see with only one eye. The patient, however, can achieve binocular vision by using both normal, heteronymous, juxta-macular fields, but only with the production of diplopia. Naturally, this diplopia, as certain of our patients demonstrated, is itself heteronymous in nature; i.e., the image from the left eye falls to the right of that from the right eye, and *vice versa*. Furthermore, if the defect in the visual fields is bitemporal, the patient will diverge his eyes so as to bring into focus the normal temporal halves of his retinæ, with a resulting divergent strabismus. This condition was observed in some of the cases presented here. Whether divergence of the visual axes becomes visible or not will depend entirely upon how far into the perimacular field the patient is forced or able to go in order to find an area of visual acuity greater than that of the macula itself.

We have been unable to find any reference to this phenomenon in the literature. Further investigation of it must wait upon the accumulation of clinical data from similar cases with more precise quantitative perimetry and scotometry, as well as careful investigation of the reciprocal functions of the external muscles of the eye.

Case Reports.

Out of a group of twenty-one cases of tumour of the hypophyseal stalk, two examples of this type of diplopia are presented here; and six examples from among twenty cases of adenoma of the hypophysis. In several other cases from each of these groups of tumours, and in one case of suprasellar endothelioma, diplopia occurred that seemed definitely to be of the same nature. These cases are not, however, included in the

report, either because essential data were not available, or else because there was some uncertainty as to the exact condition of the extra-ocular muscles.

Case 1.—*Walter A., a middle-aged man, after partial extirpation of a tumour of the hypophyseal stalk developed a progressive bitemporal hemianopia. As the progressive defect invaded the macular field, the patient developed diplopia without any extra-ocular motor palsies. As the area of macular defect became more extensive, diplopia became less distinct, the patient seeing instead only the edges of any object on which he attempted to focus both eyes.*

Walter A., an unmarried man, aged 43, was admitted to the service of Dr. Gordon Holmes on October 21, 1928. The history, the physical findings, and the presence of intrasellar opacities in the roentgenograms of the skull led to the diagnosis of a tumour of the hypophyseal stalk. This diagnosis was verified at operation on November 2, 1928. (See Beckmann and Kubie [1], Case 17).

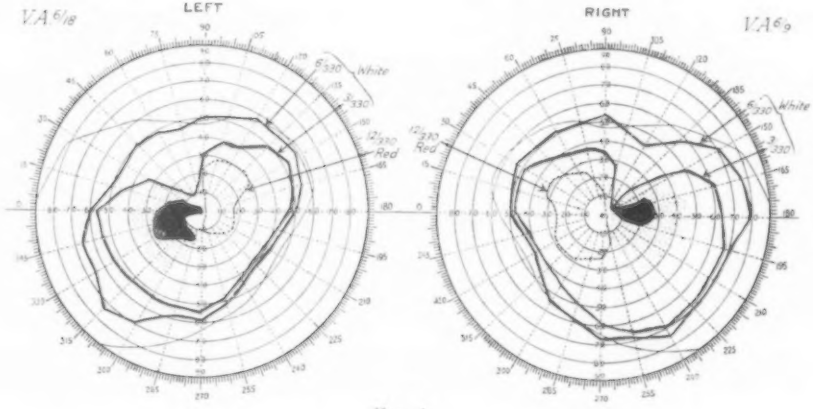

FIG. 1.

Six months earlier the patient had begun to complain of pain and a feeling of pressure in his left eye. For two months this had been relieved by glasses; but then vision in this eye became misty, especially in the outer corner. Gradually the dimness "moved across like a shutter from the left." Only one month before his admission he noticed that his right eye fatigued easily, and that his vision became blurred on reading.

On admission examination of his eyes showed a visual acuity on the right of $\frac{6}{9}$ and on the left of $\frac{6}{18}$. The fundi were normal. There was slight constriction of the temporal field of the right eye, with a defect in the upper temporal quadrant and a cæcal scotoma *that did not involve the fixation point*. In the left eye there was a more marked temporal constriction, a deeper defect in the

upper temporal quadrant and a cæco-central scotoma. The red fields showed a complete bitemporal hemianopia (see fig. 1). The external ocular movements were entirely normal and there was no diplopia.

On November 2, 1928, Sir Percy Sargent explored the base of the skull through a right frontal incision. The dorsum sellæ was found to be bulging, and after incision small masses of gelatinous and calcareous material were removed.

After a post-operative period which was complicated by intense meningeal irritation, persistent bronchitis, and delirium, the patient made a fair recovery and was discharged from the hospital on January 9, 1929. At that time his visual acuity was $\frac{6}{12}$ in the right eye and $\frac{6}{6}$ in the left. Both fields were quite full for white and red (see fig. 2). All external ocular movements were normal and there was no diplopia.

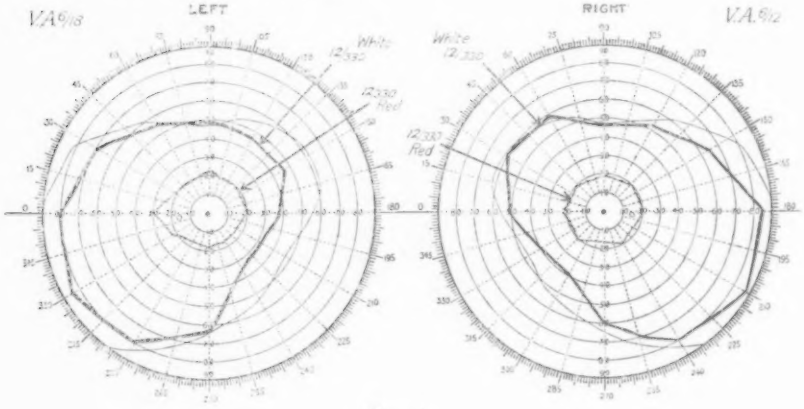

FIG. 2.

On February 8, 1929, the patient returned to the hospital for a re-examination. Visual acuity was $\frac{6}{6}$ in both eyes. The fundi were still quite normal. His only complaint at this time was of intense lancinating pains in the vertex, which usually troubled him in the early morning and then disappeared for the remainder of the day. As before there was no defect demonstrable in the movements of the eyes and there was no diplopia. His visual fields for white and for red are shown in fig. 3. The early bitemporal defect in his visual fields had not yet invaded the macular region of either eye.

Seven weeks later, on March 26, 1929, the patient was examined again. Now, however, he complained of mistiness of vision in the lateral fields, especially in the left eye ("as though a screen of gelatine were before it"), and of diplopia. He volunteered the information that he could read only with his glasses and had difficulty whenever he tried to look directly at an object, because the words or objects seemed to be vaguely doubled. On questioning, it became evident that there was little spreading of the images, that the

displacement was not increased by conjugate deviation of the eyes in any direction, and that one image was fuzzy and indistinct. The two images were so close as to be almost superimposed.

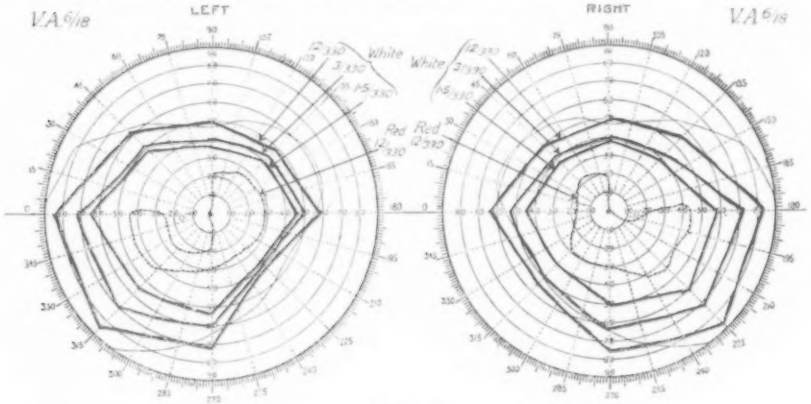

FIG. 3.

On examination, the visual acuity was found to be $\frac{6}{9}$ in the right and $\frac{6}{12}$ in the left eye; but with each eye he read only the letters on the nasal end of the line. The fundi were not changed except for doubtful pallor in the left disc. The visual fields, which are reproduced in fig. 4, showed a bitemporal

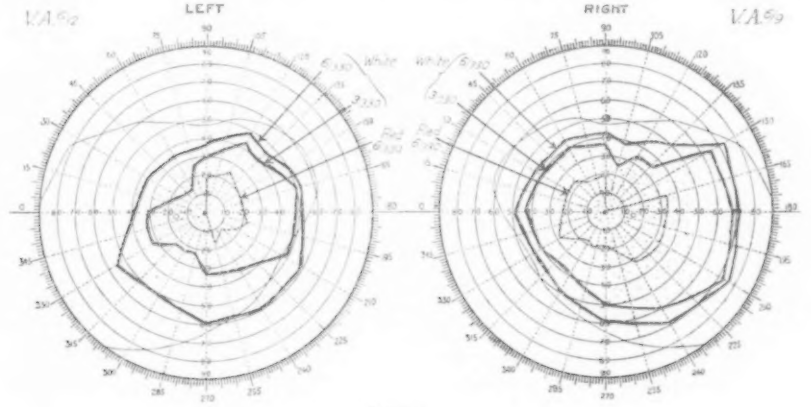

FIG. 4.

relative hemianopia for white and red, over-riding the fixation point by about five degrees. The visual acuity which the patient achieved was due not to the maculæ but to the juxta-macular nasal areas. His diplopia evidently occurred when he focused these two nasal fields upon any point.

On April 15 the patient was seen again. The visual acuity of the juxta-macular nasal fields was still $\frac{6}{6}$; but now the bitemporal hemianopia and the relative central loss had so increased that with either eye the patient could read only the nasal half of the letters at which he looked. He complained that when using both eyes he either saw double or else that he saw only the lateral edges of what he was looking at (i.e., the crossed nasal fields did not meet each other in the mid-line). His visual fields are reproduced in fig. 5. Again there was no weakness of any of the extra-ocular muscles.

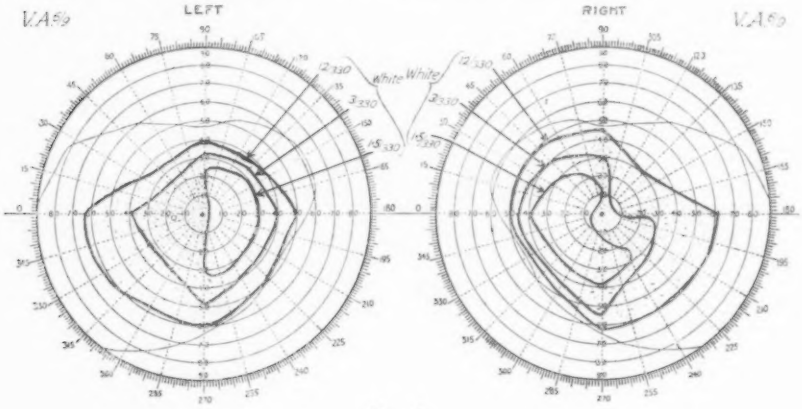

FIG. 5.

Case 2.—James W., an elderly man, had concedent diplopia, amblyopia, and bitemporal hemianopia, without extra-ocular motor palsies. The exact relationship of macular to perimacular acuity was not studied: but there is strong presumptive evidence that macular acuity was less than that of the juxta-macular nasal fields. The bitemporal hemianopia and presumptive macular defect had given rise to a slight divergent strabismus. The diplopia was heteronymous, proving that the images fell upon the nasal fields.

James W., a married man, aged 60, was admitted to the service of Dr. Gordon Holmes on August 26, 1924. The history and the physical findings led to the diagnosis of a non-acromegalic adenoma of the hypophysis: a diagnosis which was confirmed at operation two months later.

About five years before his admission to the hospital the patient had experienced some transient difficulty with his eyesight, which was relieved by glasses. Two years later, however, the difficulty had recurred and persisted. At this time he complained that his vision was not clear, but "as if smoke were floating before my eyes." This began in the left eye, but later involved the right as well; and when this occurred diplopia made its appearance. He could recall that almost from the first the images were on the same level and upright, seeming to him to be an inch or so apart. Closing the left eye made

the right-hand image disappear: and it was this right-hand image which was the less distinct (which is consistent with the earlier involvement and the more serious deterioration of vision in the left eye). To read, he had to close the left eye.

At this time he was examined in a hospital in Birmingham, and the report stated that visual acuity in the right eye was $\frac{6}{12}$, and in the left eye $\frac{6}{60}$. There was bilateral optic atrophy, and a bitemporal hemianopia. The external ocular movements were normal, despite the diplopia. No data were given as to the relation of macular to juxta-macular acuity: but his occasional complaints of the appearance of floating balls of light directly in front of him are suggestive of a macular disturbance.

On examination in the National Hospital, two years later, visual acuity in the right eye had dropped to $\frac{6}{24}$ and in the left eye to $\frac{3}{24}$. Mr. Williamson-Noble reported greyish-white pallor of both discs, more marked in the left eye. The visual fields for white are reproduced in fig. 6. Unfortunately they

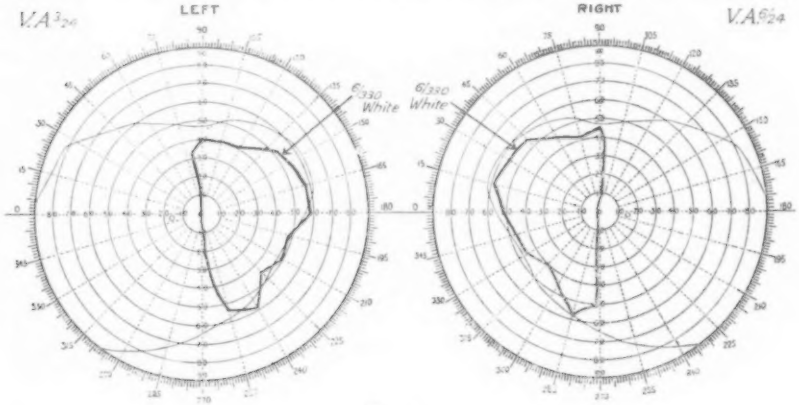

FIG. 6.

are purely qualitative, and show a bitemporal hemianopia which bisects the fixation point but fail to give any exact idea of the relative acuity of macular and perimacular vision. It was noted, however, that even with the better eye (the right), the patient had difficulty in keeping his place on a line of print, which is most readily understood on the basis of a foveal defect with a resulting tendency for the eye to wobble from one perimacular field to another (*v.i.* Discussion).

External ocular movements were found to be normal in all directions. Nevertheless there was a slight external strabismus, especially of the right eye, which is in keeping with the bitemporal field defect and the better acuity of the right eye.

On examination of the diplopia, it was found that the images were parallel, the left one sometimes slightly higher than the right, and disappeared on closing

the right eye; whereas the right-hand image disappeared when the left eye was closed. The images must, therefore, have arisen from the two nasal fields.

Case 3.—Florence S., a woman aged 50, after suffering from bitemporal hemianopia for some months, developed marked amblyopia and diplopia during a transient period of defective macular vision. When examined, some months later, the remains of the central defect were demonstrable in one eye; but the condition of the other eye could be deduced only from the history. The persistent bitemporal defect caused convergence to be poorly maintained.

Florence S., an unmarried woman, aged 50, was admitted to the service of Dr. Gordon Holmes on November 6, 1924. Her history and the physical findings led to the diagnosis of a non-acromegalic adenoma of the hypophysis, a diagnosis which was verified at operation on November 15.

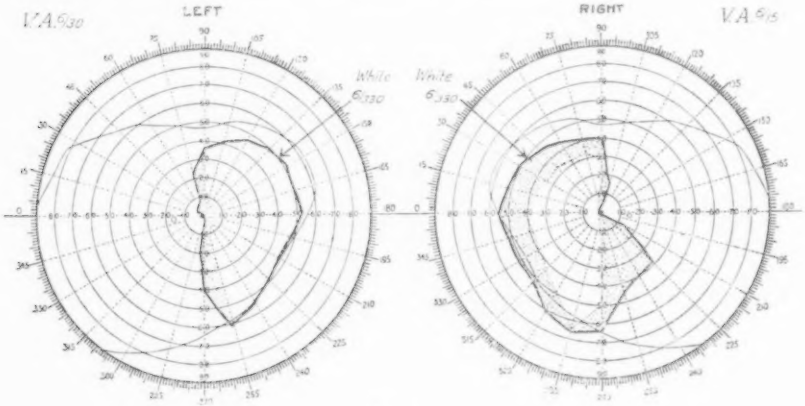

FIG. 7.

Almost three years before her admission to the hospital the patient had suffered from some ill-defined visual difficulty which had apparently been relieved by the use of glasses. Some months later, however, she noticed that she could not see well to either side. Again her symptoms decreased for several months, this time during a course of endocrine therapy. One year before her admission, however, there was a sharp reduction of visual acuity; and shortly thereafter diplopia appeared for a time. Again vision improved during a period of glandular feeding, to such a point that the patient could read quite comfortably. Finally, however, two months before she was examined in the hospital, acuity decreased and a marked bitemporal defect became manifest.

In the hospital, the visual acuity of the right eye was found to be $\frac{6}{15}$. That of the left eye is recorded as $\frac{6}{30}$; but at the same time a note is made that the letters flickered in and out of vision, so that one must conclude that macular vision was less than that of some adjacent perimacular area. Mr. Paton

reported that both discs showed temporal pallor, more marked in the left than in the right eye. The visual fields are reproduced in fig. 7. There is a bitemporal hemianopia, in the right eye apparently just reaching the fixation point, and in the left eye probably over-riding it (presumably the remains of what according to the history must have been a definite central defect).

The external ocular movements were full, synchronous and steady in all directions, except that convergence was poorly maintained, which is consistent with the bitemporal and central defects. Macular vision had so far recovered, at this time, that the only diplopia observed was a doubtful "occasional diplopia on looking at distant objects far to the right."

Case 4.—Dr. K. M., an elderly physician, had diplopia which was not referable to weakness of any external ocular muscles, associated with a bitemporal hemianopia and defective macular vision. With improvement in macular vision the diplopia ceased, despite the persistence of the bitemporal hemianopia.

Dr. K. M., a married man, aged 61, was examined by Dr. Gordon Holmes on January 1, 1927. The history and the physical findings led to the diagnosis of an intrasellar or suprasellar neoplasm. At operation, five weeks later, an adenoma of the hypophysis was found and histologically verified.

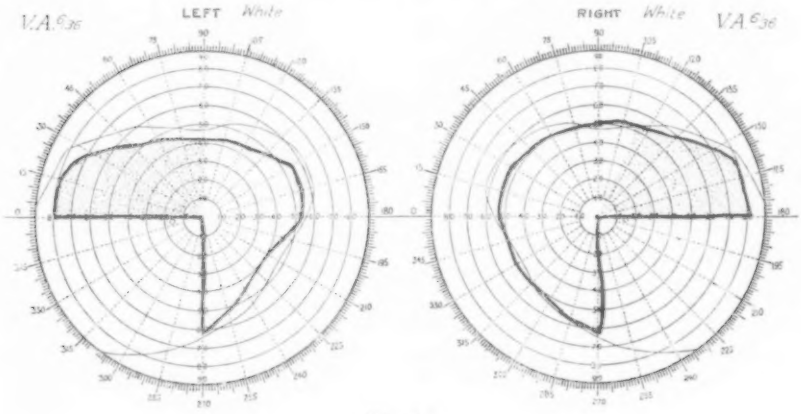

FIG. 8.

When examined by Dr. Holmes the patient had no diplopia, and no weakness of the external ocular muscles. The visual fields showed a bitemporal loss which spared the fixation point so completely that visual acuity was $\frac{6}{6}$ in the right eye and $\frac{6}{9}$ in the left. Both discs were pale, however, and the history, and the charts of previous perimetric examinations, which the patient brought with him, indicated that there had been earlier periods of more extensive visual defect.

Three years before coming to Dr. Holmes the patient had had vague visual difficulties, and after these had existed for twelve months diplopia developed. Despite the fact that the patient was a physician and could give a very accurate story, the description of the diplopia did not point to a weakness of any of the external ocular muscles. In addition to the diplopia there was a definite history both of a macular and of a temporal defect in each eye, since the patient could see only the nasal half of an object at which he looked, and in trying to read he had to lay a straight edge under the line which he was following in order to keep his place. As further evidence of the existence of a macular defect at this time is the fact that the question was raised among the ophthalmologists whom he had consulted as to whether he might have perimacular hæmorrhages. This was finally denied. At that time visual acuity was about $\frac{6}{18}$. The visual fields recorded during this period are reproduced

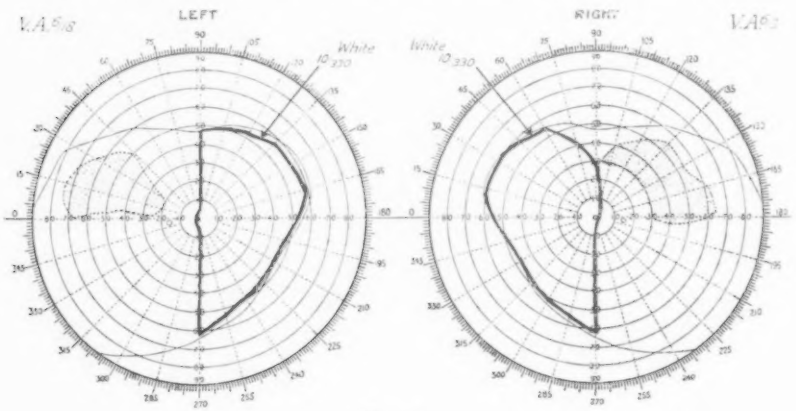

FIG. 9.

in fig. 8, and show a complete inferior temporal loss in both fields, with a relative superior temporal amblyopia. The exact condition of macular vision is not made clear by these purely qualitative fields. Later fields demonstrate a gradual progression to a practically complete bitemporal hemianopia, but the history and examination show that, synchronously with this, macular vision (and visual acuity) improved, and as a result the diplopia disappeared (fig. 9).

Case 5.—Louisa N., a young woman, was seen after several years of progressive deterioration of vision associated with diplopia. There was no extra-ocular motor palsy. Vision was lost except in the upper nasal quadrant of each eye. The patient could produce diplopia at will by attempting to focus these two fields upon a bright light.

Louisa N., an unmarried woman, aged 27, was admitted to the service of Dr. W. J. Adie on December 1, 1925. The history and the physical findings pointed to the presence of a suprasellar neoplasm, and some weeks later a

typical adamantinomatous cyst of the hypophyseal stalk was exposed at operation. (See Beckmann and Kubie [1] Case 9.)

Visual difficulties had begun insidiously about ten years before her admission to the hospital. Of their exact nature little is known. Amblyopia had affected the right eye first, but then had improved in this eye, only to appear in the left eye, where it progressed rapidly almost to blindness. Eventually vision deteriorated in the right eye as well. At some time, during the development of this condition, diplopia had appeared; but for one year prior to her admission spontaneous double vision had ceased. It was noted, however, that the patient could still "cause diplopia on voluntary effort" (i.e., with the effort to use binocular vision).

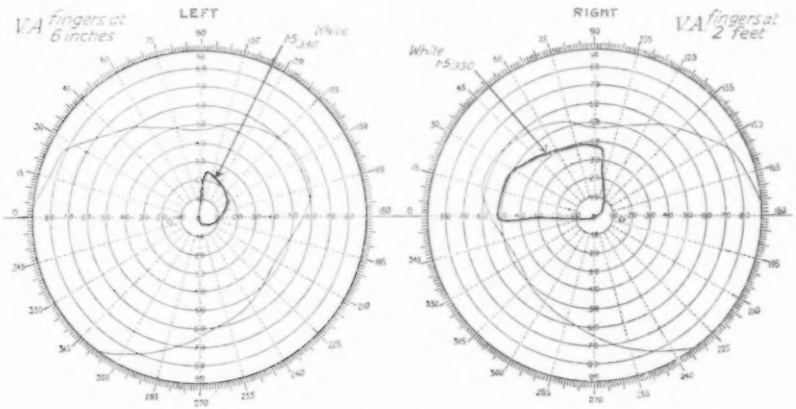

FIG. 10.

On examination it was found that central acuity was reduced to counting fingers, at 6 in. in the left eye, and at 2 ft. in the right. Mr. Williamson-Noble reported that both discs were pale, with sharply-defined edges, clear laminæ cribrosæ, and normal vessels. The visual fields are reproduced in fig. 10. They demonstrate the persistence of an island of imperfect vision in the upper nasal quadrant of each eye. The relationship of macular to perimacular acuity within these islands is not shown.

All external ocular movements were full, steady, and synchronous in all directions. Nevertheless, it was noted that she had diplopia when concentrating on a light in any direction except to the left (where it passed out of the field of vision of the left eye completely).

Case 6.—*Edie A. W., an elderly woman, suffered from persistent diplopia and amblyopia. The history does not furnish full details of the development of the condition. There was an extensive temporal defect in one eye which*

included the fixation point; and a deep upper temporal quadrantic defect in the other with an absolute cæco-central scotoma. There was no extra-ocular motor-palsy.

Edie A. W., an unmarried woman, aged 57, was admitted to the service of Dr. Gordon Holmes on May 21, 1926. The history and the findings led to the diagnosis of an adenoma of the hypophysis without acromegaly, and at operation, one month later, this diagnosis was verified.

Vaguely for ten years, and more insistently and definitely for five years, the patient had suffered from diplopia. This occurred chiefly during efforts to use her eyes for fine work. She said that, "Words would drop and get out of place; numbers would get mixed up." She was not aware, subjectively, of any temporal loss. The doubled images sometimes seemed to be side-by-side and close together. Three years before her admission the reduction in acuity became more noticeable, with progressive inability to read, and pain in the eyes and burning headaches. Beyond this the history furnishes no details.

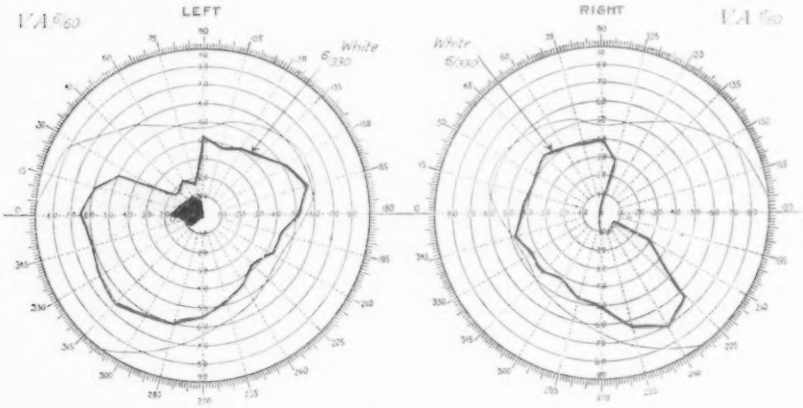

FIG. 11.

On examination, her visual acuity was found to be reduced to $\frac{6}{60}$ in both eyes. Mr. Williamson-Noble reported that there was general pallor of both discs, more marked in the left eye. The fields are reproduced in fig. 11. In the right eye there was a deep defect in the upper temporal quadrant which included the fixation point and invaded the inferior temporal field. In the field of the left eye the absolute defect in the upper temporal quadrant was less extensive, but the relative dimness involved most of the temporal field, and in addition there was a small, absolute cæco-central scotoma.

All external ocular movements were full, steady and synchronous. For this reason the story of diplopia was discounted and no close scrutiny or examination of the condition was made.

Case 7.—Dorothy M., a young woman, passed through periods of recurrent and deepening amblyopia, with loss first of the left temporal field and then of the right. After an episode of scintillating central scotoma, colour vision and central acuity became dim, and diplopia developed, without extra-ocular motor palsies. With recovery of central vision the diplopia disappeared, despite the persistence of a bitemporal hemianopia.

Dorothy M., an unmarried girl, aged 18, was admitted to the service of Dr. Gordon Holmes on June 15, 1927. The history and physical findings led to a diagnosis of a non-acromegalic adenoma of the hypophysis. On July 4 this diagnosis was confirmed at operation.

Five months before admission she noticed that after reading for any length of time her vision blurred. The left eye was more seriously involved than the right; and within a day or so she began to experience difficulty in seeing objects to her left. At the same time headaches, from which she had suffered for some months, became worse and were accompanied by flashes of blue light which appeared in one eye at a time, more often in the left than in the right.

Six weeks after the onset she developed definite difficulty in seeing things that were on her right side, and there was marked reduction in the acuity of her colour vision. Within a few weeks after this she began to notice that she was seeing double. This was almost continuous for two weeks, then became intermittent, and finally disappeared several weeks before she entered the hospital. No exact analysis of the relationship of the images was obtainable.

In the hospital, the visual acuity was found to be $\frac{6}{18}$ in the right eye and $\frac{3}{6}$ in the left. The charts of the visual fields before operation are incomplete; but rough tests, carefully done, revealed a bitemporal hemianopia. Macular vision was more acute than perimacular vision, objects suddenly becoming clearer at the fixation point. The right fundus was found to be normal by Mr. Paton, but the left showed temporal pallor of the optic disc.

There was no diplopia at this time, and the third, fourth and sixth nerves showed no abnormality.

The disappearance of the diplopia, despite the persistence of the bitemporal hemianopia, is easily explained by the marked improvement in macular acuity, especially in the left eye.

Case 8.—Annie H., an elderly woman, had progressive dimness of vision, and then diplopia without weakness of the extra-ocular muscles. The diplopia was most evident on efforts to read. Loss of temporal fields was noted early on one side; but was not observed by the patient in the other eye until vision in the first had almost gone. In this case the coincidence of the bitemporal hemianopia and the reduction of macular vision with the appearance of the diplopia is only presumptive, from the history, since the patient first came for examination three years after one eye was quite blind. All extra-ocular movements were normal; but the long-standing bitemporal defect had caused a slight divergent strabismus.

Annie H., a married woman, aged 50, was admitted to the service of

Dr. S. A. Kinnier Wilson on January 30, 1922. The history and the physical findings pointed to the existence of an adenoma of the hypophysis without acromegaly. This diagnosis was verified at operation and autopsy a few weeks later.

For several years the patient had suffered from progressive dimness of vision. At first distant objects were difficult to see; then diplopia appeared. The patient claimed that in a word of three letters, such as "MEN," the middle letter "E" would be seen doubled. Or two men approaching her in the street might appear as three. The third image was always indistinctly superimposed upon the other two, and she could not tell "which man had been doubled." At times the last word in a line of print might seem to be on a higher level than the rest of the words.

At about the same time, or immediately after the onset of this diplopia, the patient first became aware of the loss of her temporal fields, especially on the left side. It was not until the left eye became quite blind, however, three years before her admission, that she became fully aware of the temporal loss on her right side. With the blindness of her left eye the diplopia had disappeared.

On examination, the blindness of the left eye was confirmed; and visual acuity of the right eye was found to be reduced to $\frac{6}{9}$. There was a complete right temporal hemianopia, to rough tests, passing vertically through the fixation point.

No charts of this condition are found in the record. Mr. Paton reported that both discs were quite white, with clear edges.

There was a slight but definite divergent squint, quite compatible with the bitemporal field defects which had existed in both eyes and which persisted in the seeing eye. All external ocular movements were full, steady, and synchronous, however.

DISCUSSION.

In binocular vision the fusion of images formed in the two eyes depends upon the use of corresponding points of the two retinæ. If anything occurs to alter the normal synergic movements of the two eyes, so that the portion of the retina of one eye on which the image falls is not homologous with that of the other, diplopia results. Hitherto, there has been only one recognized cause for such a failure of the two eyes to work together, i.e., a palsy of one or more of the extra-ocular muscles. In the cases described in this report, however, repeated instances are given of diplopia occurring without there being any weakness of the eye muscles. On the contrary, the diplopia seems to result from the attempt of the normal extra-ocular muscles to compensate for defects in the visual fields and in macular acuity by deliberately bringing into simultaneous use portions of the retinæ which had hitherto been unassociated.

The mechanism of this type of diplopia is allied to the phenomena which are observed in coal-miners' nystagmus. This is a condition which occurs in men who have worked for many years in coal mines in which the illumination is so dim that in the dark-adapted eye the visual acuity is greater in the perimacular region than at the macula itself (Medical Research Council: First Report of the Miners' Nystagmus Committee, 1922 [4]; Llewellyn [3]). As a result the eye of the miner comes to depend upon perimacular rather than macular vision. But since there is no single spot in the perimacular retina, the visual acuity of which is greater than all the rest, and since the perimacular retina is subject to rapid fatigue, a tendency arises to roll the eyes frequently from one point of temporary fixation to another. (Cridland [2] suggests, on p. 701, further data on this tendency which is not, however, relevant to our problem.) It must be emphasized that in the absence of defects in the visual fields or of extra-ocular motor palsies, the eyes move with parallel axes. Therefore in uncomplicated cases of miners' nystagmus homologous parts of the retinæ are always in use and no diplopia occurs. Llewellyn [3] could find but two cases of diplopia in 600 instances of this disease, and believes these to have been the result of extraneous factors.

In the cases reported here it was not poor illumination, but damage to the macular bundle, which lowered the visual acuity of the macula below that of the surrounding retina. The result was similar, in that clearer vision was sought by using perimacular fields. But unlike the sufferers from miners' nystagmus these patients could not use homologous parts of their retinæ because of the bitemporal defects in their visual fields. Diplopia from the use of heteronymous fields was therefore inevitable.

On the other hand, closely analogous to the oscillations of the eyes in miners' nystagmus was the complaint of some of our patients that the double images "wobbled." Cases 2 and 4 could not keep their eyes focused on a line of print without laying a straight ruler to guide them. Case 6 was troubled because "words would drop and get out of place; numbers would get mixed up." Case 8 observed that the relative positions of the two images would keep shifting.

This type of diplopia was actually observed and examined only in Cases 1, 2 and 5. In Case 1 the patient was watched through the successive stages of a rapidly advancing bitemporal defect; and it was seen that diplopia developed without weakness of any extra-ocular muscles, only as the macular areas of both eyes were encroached upon.

This condition persisted for two weeks, and then progressive failure of vision eliminated the diplopia.

In Case 2 it was possible to prove that the double images arose from the two nasal fields, since the diplopia was heteronymous and the temporal fields were blind. This fact fully explains the existence of a slight divergent strabismus; because this position would bring into simultaneous use the two temporal retinæ (i.e., nasal fields).

Case 5 affords, perhaps, the clearest evidence of any that our interpretation of this diplopia is correct. This patient was almost blind, except for islands of partial vision in both upper nasal quadrants. When the eyes were relaxed there was no diplopia. But whenever the patient deliberately attempted to focus both eyes on a bright light diplopia occurred at once, demonstrating that under these conditions the normal synergic patterns of the eye movements can be supplanted by voluntary divergence of the visual axes, so as to bring into play both nasal fields for binocular vision. By this divergence of the visual axes areas of greater acuity could be used and binocular vision was achieved; but because heteronymous visual fields were employed a crossed diplopia resulted.

In Cases 3, 4, 6, and 7 the period of diplopia had passed before the patient came under observation; but in each case the history and the residual findings were reasonably convincing that the patient has gone through a stage of bitemporal hemianopia with reduction of acuity at the maculæ. Case 8 is presumably an example of the same condition, but here the history is not entirely complete, and the patient was blind in one eye and nearly blind in the other when she came under observation.

Summary.

(1) The occurrence of true diplopia without any weakness of the extra-ocular muscles is described in six cases of adenoma of the hypophysis and two cases of tumour of the hypophyseal stalk.

(2) In all of these cases there was a bitemporal hemianopia; in none of them was there an homonymous type of defect in the visual fields.

(3) In some of the cases it was possible to demonstrate, and in others it was possible to infer from the histories, that visual acuity at the macula was less than that of the juxta-macular nasal field (i.e., the temporal retina).

(4) In certain cases it was clear that the diplopia was heteronymous, the images evidently arising from the nasal fields. In other cases the

images were too close together, or too indistinct, to permit of such exact analysis.

(5) In no case was the diplopia increased by conjugate deviation of the eyes; but rather by efforts to focus both eyes for clearer binocular vision in any direction.

(6) The diplopia must depend, therefore, upon the fact that in the presence of impaired macular vision the patient attempts to use the adjacent areas of the retina in which visual acuity is greater. Since there is a co-existent bitemporal hemianopia, however, the only available fields are the two nasal fields. To secure binocular vision of good acuity he must employ these. Since, however, these are not homologous parts of the retina, diplopia inevitably results. In order to bring into focus his two nasal fields, he must to some extent diverge his visual axes. Whether this divergence will be visible or not will depend upon how far into the perimacular field he must go to find greater visual acuity.

(7) In keeping with this interpretation; certain of the cases showed a slight divergent strabismus without any accompanying weakness of convergence or of internal rotation of either eye on conjugate lateral movements.

It is a privilege to express our gratitude to Dr. Gordon Holmes for his advice in the preparation of this report. We wish, further, to thank the Medical Committee of the National Hospital for their permission to use the records of the cases included here.

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STUDIES ON THE OPTIC THALAMUS OF THE INSECTIVORA.—THE ANTERIOR NUCLEI.

BY W. E. LE GROS CLARK, D.Sc.

Introduction.

In a recent paper [8] dealing with the study of the thalamus in the tree-shrew, a primitive and generalized insectivore, it was emphasized that the comparative study of the mammalian thalamus and the homologization of the various thalamic nuclei which have been described are rendered very difficult partly because of the lack of sufficiently detailed accounts of the structure of the thalamus in the different mammalian groups. The development and differentiation of these nuclei show a very considerable degree of variation in different groups of mammals, and this is so even within the limits of a relatively small group of simple animals such as the insectivora. For a comparative study of the thalamus, the brains of the insectivora are especially useful. They are small, relatively generalized brains, and readily comparable in their size. At the same time they show marked specific characteristics in which they contrast with each other. Such a differential development of the cerebrum as a whole is reflected to a large extent in the structure of the thalamus, and it seems feasible to surmise that a comparative study of these brains may yield evidence of an anatomical nature concerning the significance of the different thalamic nuclei.

Of the nuclear masses which make up the thalamus, the anterior group of nuclei can usually be fairly readily distinguished and identified. But the wide variation in the relative degree of development of its several elements may give rise to considerable difficulties. It will be well here to anticipate the subsequent discussion of the observations which have been made, and to define the anterior nuclei of the thalamus as those groups of cells situated in the antero-dorsal region of the thalamus, and in connection with which the fibres of the mammillothalamic tract (bundle of Vicq d'Azyr) terminate. This definition may be regarded as holding even though in some mammals in which one of the elements is relatively poorly developed it may not be possible by ordinary methods actually to trace the terminal fibres of this tract into it. Three

elements of the group are recognized, and each of them, when well developed, is found to receive mammillothalamic terminals. The three elements, with their synonyms, are as follows, using the nomenclature adopted by Gurdjian [10] in his work on the diencephalon of the rat:—

Nucleus anterodorsalis (angular nucleus of Cajal, n. anterior C of Monakow and others, n. anterior B of Winkler and Fortuyn, n. triqueter of Livini and Rothig, n. disseminatus of Sachs, Brunner and Spiegel, and Woollard, n. dorsomedialis of Papez, ? part of n. reuniens of Malone).

Nucleus anteroventralis (dorsal nucleus of Cajal, n. anterior A of Monakow, Winkler, Fortuyn and others, n. anterior of Papez, Pines and others, n. dorsalis magnus of Sachs and others).

Nucleus anteromedialis (included among the medial group of nuclei by most authors).

Material and Methods.

The brains of four species of insectivora have been used for the study of the thalamus. The characteristics of these brains have been described elsewhere [5, 6, 7], but the salient features which distinguish them may be briefly indicated (fig. 1).

Erinaceus europæus (hedgehog). — The primary and secondary olfactory centres of the brain are very well developed, especially the olfactory bulb and the piriform lobe. The dentate gyrus is conspicuous and forms a convoluted strip of cortex on the medial surface of the cerebrum. The corpus callosum is small and of primitive type, while the ventral commissure is relatively large. The neopallium forms but a small proportion of the cortical surface. The optic nerves are very small and the visual cortex poorly differentiated.

Macroscelides (elephant-shrew).—The olfactory bulb and the piriform lobe are relatively smaller, though quite well developed. The hippocampus shows an extraordinary development, especially the subsplenial portion, and out of all proportion to the secondary olfactory centres. This enlargement of the hippocampus has led to a distortion of the neopallial and hippocampal commissures. The corpus callosum has become stretched out to form a long, attenuated commissure, and is clearly separated from the fornix commissure which, in section, assumes the crescentic form characteristic of marsupial brains. The optic nerve is large, and the anterior colliculus enormous. The visual area of the cortex, however, is poorly differentiated. The retrosplenial area of the cortex, which in most mammalian brains is limited to a small area in

relation to the splenium of the corpus callosum, extends over a considerable area and reaches on to the dorsal surface of the neopallium.

Ptilocercus lowii (pen-tailed tree-shrew).—This is a generalized brain showing a moderate development of the olfactory bulb and piriform lobe. The hippocampal formation is also moderately developed, and shows a well-marked subsplenial flexure. The corpus callosum is elongated, and the ventral commissure is small.

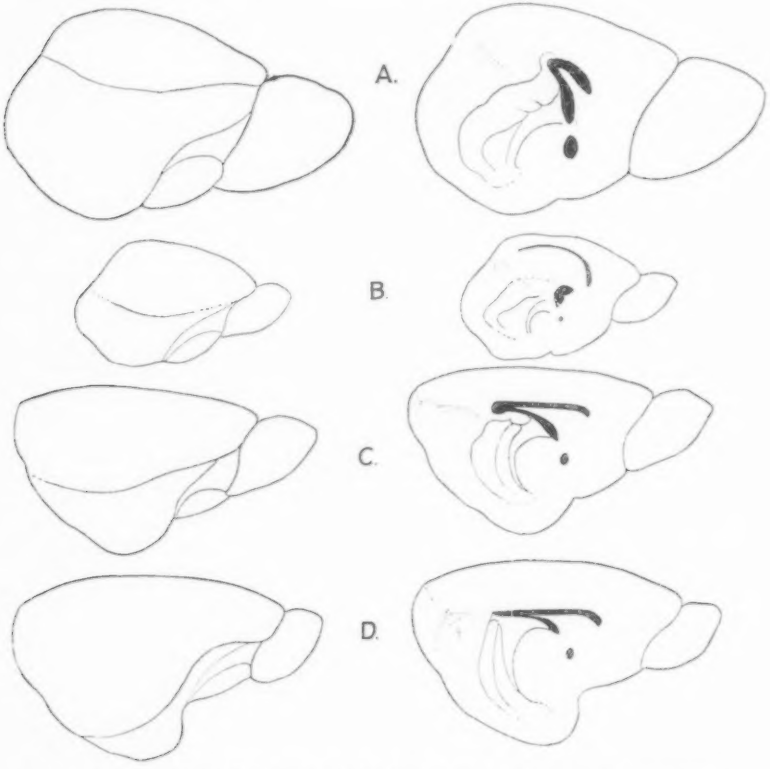

FIG. 1.—Lateral and medial views of the brains of four species of insectivores. (*a*) *Erinaceus*. (*b*) *Macroscelides*. (*c*) *Ptilocercus*. (*d*) *Tupaia minor*. (× 2½.)

Tupaia minor (lesser tree-shrew).—In this brain there is a diminution of the olfactory bulb and piriform lobe. A reduction of the hippocampal formation is also indicated by the absence of any subsplenial flexure. The corpus callosum is elongated and shows no splenial thickening, the ventral commissure is small and the fornix commissure somewhat

reduced in comparison with the other insectivore brains. The neopallium is much better developed and forms definite occipital and temporal poles. The optic nerve is large, and the anterior colliculus is very large, especially in comparison with the reduced size of the posterior colliculus. Unlike the other brains, the visual cortex is well differentiated and extensive. There is also an indication of the sulcus calcarinus.

The thalamus has been studied by series of coronal sections, and in the case of *Erinaceus* with sagittal sections also, one or more series of each being stained with toluidin blue, and one with iron-hæmatoxylin. The latter series are of considerable aid in the interpretation of the cyto-architecture of the thalamus and allow the relations of the thalamic nuclei to the main fibre tracts to be studied. It is clearly not possible, however, by these methods to give a detailed and finished account of the whole of the fibre connections of the nuclear groups.

In the descriptive account, planes have been indicated in an antero-posterior direction by giving the numbers of the sections. These sections have been numbered from before backwards, the first section being taken as that in which the anterior nucleus first appears rostrally. In order to give a correct impression of the anteroposterior extent of the thalamus, below are tabulated the number of sections of each series from which the descriptions have been given from Section 1, as far caudally as the anterior limit of the posterior commissure, together with the thickness at which the sections were cut:—

Erinaceus.—61 sections at 15μ, every fourth section mounted.

Macroscelides.—107 sections at 15μ, every section mounted.

Ptilocercus.—157 sections at 15μ, every section mounted.

Tupaia minor.—123 sections at 12μ, every alternate section mounted.

TEXT FIGURE ABBREVIATIONS.

Ad	N. anterodorsalis	M T	Tractus mammillothalamicus
Am	N. anteromedialis	N R	Nucleus reticularis
Av	N. anteroventralis	O C	Optic chiasma
A C	Anterior colliculus	O H	Tractus olfactohabenularis
C Ad	Commissura interantero dorsalis	O T	Optic tract
Dm	N. dorsomedialis	P C	Posterior colliculus
F	Fornix	P C M	Pedunculus corporis mammillaris
F R	Fasciculus retroflexus	Re	N. reuniens
G C	Commissure of Ganser	S M	Stria medullaris
H	N. habenulæ	Va	Anterior ventral nucleus
L	N. lateralis (pars anterior)	Vp	Posterior ventral nucleus
L G	Lateral geniculate body	V C	Ventral commissure
M G	Medial geniculate body		

Tupaia minor. (Fig. 2.)

The elements of the anterior group of nuclei in the thalamus of this animal can readily be homologized on the basis of cyto-architecture with those which have been described in other mammals.

The *anterodorsal nucleus* is conspicuous for the fact that its constituent cells are closely packed together and are more darkly stained in toluidin blue sections than those of the other nuclei. The cells are rounded, oval, and subangular, rather smaller towards the anterior end and the lateral part of the nucleus than elsewhere, and not larger than those of the anteroventral nucleus. The nucleus first becomes evident in this series of transverse sections when traced cranio-caudally at about

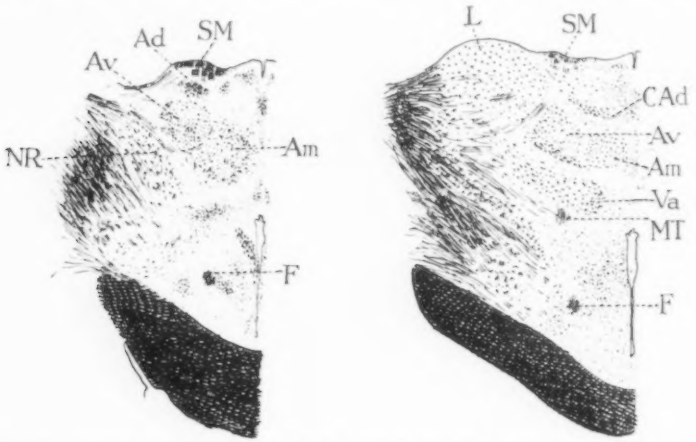

FIG. 2.—Coronal sections (23 and 38) of the thalamus of *Tupaia minor*. (× 10½.)

section 18, where it forms a narrow crescentic cap covering the upper surface of the ventral element. Here it lies immediately subjacent to the stria medullaris and extends inwards towards the nucleus parataenialis. The long axes of the oval cells are usually disposed concentrically with the circular anteroventral nucleus. By section 25, its medially-placed cells show a tendency to drift towards the median plane preparatory to the formation, in a slightly more caudal plane, of a commissural nucleus, and here it comes into relation laterally with the anterior extremity of the lateral thalamic nucleus (nucleus lateralis A). By section 30, it forms an oblique band of cells reaching dorsolaterally almost to the dorsal surface of the thalamus and extending ventromedially towards the median line. It now rapidly diminishes in size. Some few

of the characteristic cells of the nucleus may be seen extending across the midline to form a bed nucleus for the interanterodorsal commissure but by section 40 all recognizable trace of this has disappeared. Throughout its extent, the anterodorsal nucleus is richly permeated with bundles of medullated fibres passing up to the stria medullaris, and it may be here noted that this intimate topographical relation of the nucleus with this fibre tract is a very characteristic feature to be found in the other forms examined. Laterally the nucleus is reached by contributions from the superior thalamic radiations.

The *anteroventral nucleus* appears in advance of the previously described element in these sections. At its anterior extremity it is bounded dorsally by the stria medullaris and ventrolaterally by the nucleus reticularis. The nucleus is composed of cells of a type similar to those of the dorsal element, except that they are not so darkly stained and, also, they are much more scattered in their arrangement. In many toluidin blue sections it is impossible to separate the anteroventral from the anteromedial nucleus, especially rostrally. In myelin-stained sections, however, the distinction is clearer. The nucleus is penetrated on its lateral aspect by contributions from the superior thalamic radiations, and many of these fibres tend to encapsulate the nucleus by flowing round its periphery. The lateral olfactohabenular fibres, on their way dorsalwards to join the stria medullaris, further add to this encapsulating effect and thus help to define the outline of the nucleus. The anteroventral element reaches its maximum size in transverse section between sections 25 and 30, and, a few sections more caudally, it blends with the anteromedial nucleus and loses its individuality. In the ventrolateral region of the nucleus, the component cells where they lie up against the internal capsule are rather smaller than elsewhere. Here, also, they are more oval in shape with a tendency to be disposed with their long axes directed medioventrally, evidently in association with commissural fibres of the anteroventral and lateral nuclei. In sagittal sections, the anteroventral nucleus is well defined by the termination of the mammillothalamic tract and in this plane it is also circular in shape.

The *anteromedial nucleus* is hardly to be defined in myelin stained sections. On the basis of cytoarchitecture, however, it can be recognized with little difficulty, though, as stated above, in many sections it runs without interruption into the anteroventral element. Its constituent cells are quite similar to those of the anteroventral nucleus. Rostrally, the nucleus does not extend to the midline. Caudally, it extends medially and meets its fellow of the opposite side at about section 40. Thereafter, it rapidly disappears.

The *mammillothalamic tract* can be readily followed throughout its course in the transverse and sagittal (fig. 9) series of sections. In the latter it is seen to be a long drawn-out tract of even width running first dorsally and then bowed forward by the anterior convexity of the ventral group of nuclei. It terminates mainly in connection with the anteroventral nucleus. Some of its medial fibres, however, can be traced into ultimate relation with the anteromedial element. No fibres of the tract could be demonstrated actually to reach the anterodorsal nucleus.

Ptilocercus. (Fig. 3.)

In this tree-shrew, the anterior nuclei are readily comparable with those of *Tupaia* and chiefly differ in the relatively greater size of the dorsal and ventral elements.

The *anterodorsal nucleus* consists of medium-sized rounded or subangular cells with darkly staining cytoplasm, closely packed together in the usual characteristic manner. The cells are in general somewhat larger than those of the anteroventral nucleus. Rostrally, however, its component cells are smaller and more rounded than elsewhere, and here the limits of the nucleus are not well defined. It first becomes distinct at about section 20, where it forms a fairly thick crescentic cap of cells with a ventral concavity surmounting the circular anteroventral nucleus. It is bounded dorsally by the stria medullaris and medially by the parataenial nucleus, while laterally the cells, which here are more scattered, are related topographically to the superior thalamic radiations. By section 30, the nucleus has increased slightly in size and the component cells are larger and more uniform. Laterally it has now come into contact with the anterior end of the lateral nucleus. Further caudally, it diminishes and, by section 40, forms a small rounded clump of cells. A few sections more posteriorly it disappears, some of its cells apparently being displaced towards the midline where they form a slender and indistinct bed nucleus for a commissure. Anteriorly, the anterodorsal nucleus is related rostrally and laterally to the thick lateral olfactohabenular tract, many of whose fibres run through the anterior extremity and lateral part of the nucleus as discrete bundles. The smaller size of the constituent cells in these regions seems to be associated with this denser penetration by the fibres passing up to the stria medullaris. More caudally, the nucleus is still penetrated by these fibres, but in smaller bundles. Laterally, it is related to the thalamic radiations, some of whose fibres enter it. The nucleus also appears to

be connected with the subjacent anteroventral nucleus by finer bundles of inter-connecting fibres.

The *anteroventral nucleus* consists of cells of the same type as, but rather smaller than, those of the anterodorsal element. They are also more lightly stained and more scattered in their arrangement. Towards the lateral aspect of the group, the cells tend to be smaller and more closely packed, and in some sections show an obscure lamination as the result of the passage through this part of the nucleus by contributions from the superior thalamic radiations. The nucleus first appears rostrally as a circular group of cells fairly close to the midline. In myelin-stained sections it is quite sharply defined with an even contour

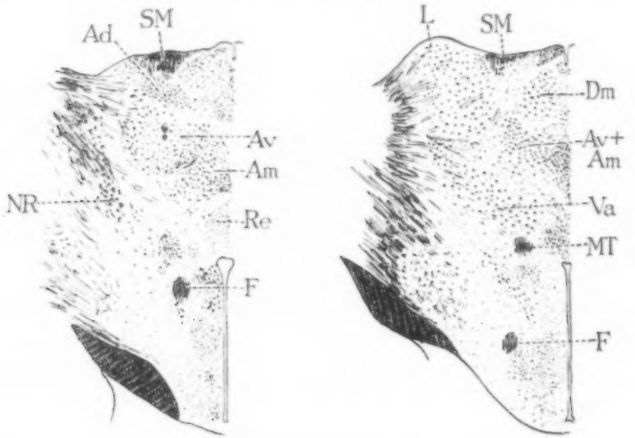

FIG. 3.—Coronal sections (21 and 58) of the thalamus of *Ptilocercus*. (× 10½.)

by a capsule of medullated fibres. Here it is bounded laterally by the greater bulk of the lateral olfactohabenular tract, many of whose medial fibres appear to sweep round the nucleus to form a capsule for it. Some of its fibres, however, enter its ventral aspect and pass through it on their way dorsally to the stria medullaris. Between sections 20 and 30, the nucleus reaches its maximum size in transverse section and is of regular circular shape. Here it reaches close to the midline and is penetrated laterally by fibres of the superior thalamic radiations. Dorsolaterally it is in relation with the lateral nucleus of the thalamus and ventromedially with the anteromedial nucleus. By section 40, it has become much diminished in size and appears to have been displaced medioventrally by the enlarging lateral and dorsomedial nuclei. It now

loses its individuality, merging with the anteromedial element, while its constituent cells become arranged in rows curving towards the midline and forming evidently a bed nucleus for a commissure which crosses by the massa intermedia of the thalamus.

The *anteromedial nucleus* consists of cells of the same type as those of the ventral element, but as a general rule very slightly larger. It is poorly differentiated and small, being wedged in between the medioventral border of the anteroventral nucleus and the midline. It may be distinguished from the anterior paraventricular nucleus or nucleus dorsalis raphae by the larger size of its cells and by their more scattered disposition. It is connected with its fellow of the opposite side across the midline and caudally it merges with the anteroventral nucleus as described above. Its caudal limit is very difficult to define, but it can no longer be recognized caudal to section 60.

The *mammillothalamic tract* cannot be followed in these preparations to their ultimate termination. It is clear, however, from the direction in which this tract is running that it is mainly associated with the large anteroventral element of the group of anterior nuclei. The relative size of the anteromedial element indicates that if any fibres terminate in it they must be relatively few.

Macroscelides. (Fig. 4.)

The appearance of the anterior nuclei of the thalamus in this aberrant insectivore is very different from those already described, and it would be difficult to homologize the elements except by tracing the connections of the mammillothalamic tract.

The *anterodorsal element* (fig. 5) consists of very large angular and subangular cells with darkly staining cytoplasm. The nucleus is relatively lightly stained and the nucleolus is conspicuous. The cells are closely packed together in a matrix which is throughout permeated with an intricate network of fine medullated fibres and penetrated by bundles of fibres passing dorsally to the stria medullaris. In all sections the nucleus is extremely well defined with an even rounded contour and surrounded by what may be called a "lymph space." Anteriorly it appears in the transverse sections in advance of the other elements of the anterior group of nuclei and immediately caudal to the point where the lateral olfactohabenular tract curves dorsally and backwards to contribute to the stria medullaris. Here it lies close to the dorsal surface of the thalamus, bounded dorsomedially by the large stria medullaris, medially by the nucleus paratænialis, ventrally by the anterior column

of the fornix, and laterally by the stria terminalis and its bed nucleus. Traced caudally, the nucleus soon assumes a regular oval form with the long axis directed medioventrally and comes into relation laterally with the anterior extremity of the lateral geniculate body. It reaches its maximum size in transverse section at about section 20. Although its constituent cells maintain their characteristic features, towards the dorsal pole of the nucleus they are found to be rather smaller, more darkly stained and more closely packed together. The nucleus is penetrated freely by bundles of fibres from its lateral and ventral aspects which can be traced laterally into the thalamic radiations and ventrally to the lateral olfactohabenular tract. It seems that most of these bundles of fibres pass through the nucleus to reach the superjacent stria

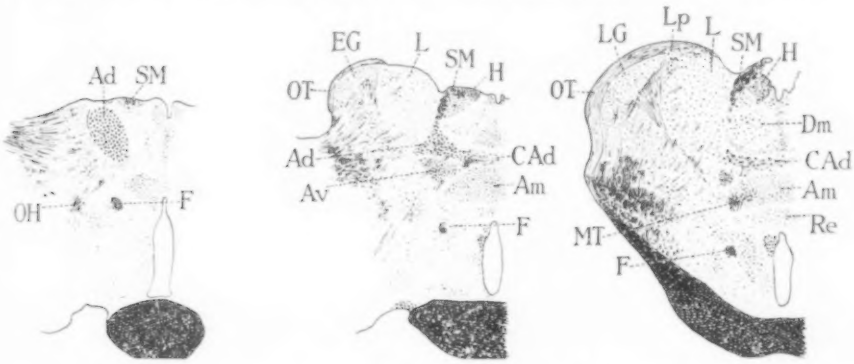

FIG. 4.—Coronal sections (18, 41 and 66) of the thalamus of *Macroscelides*. (× 8.)

medullaris, and it seems impossible to avoid the conclusion that there is therefore a contribution from the thalamic radiations to the stria medullaris in *Macroscelides*. There is no doubt, also, that some of the fibres entering on the lateral aspect, and therefore derived from the region of the internal capsule, contribute to the intercellular network of the anterodorsal nucleus. Further, these sections would seem to indicate that fibres from the intercellular network of the nucleus emerge and pass into the stria medullaris. However the material may be interpreted, there is a very intimate association between the anterodorsal nucleus and the stria medullaris.

By section 25, the nucleus in transverse section has become triangular, being flattened on its lateral aspect by its apposition to the anterior extremity of the lateral thalamic nucleus and ventrally by contact with the anteroventral nucleus. Here, from its medial angle

emerge a large number of medullated fibres which cross the midline, forming a commissure which is of conspicuous breadth in the antero-posterior as well as in a dorsoventral direction. The nucleus now appears to be approaching the midline and, by section 30 (with the appearance of the lateral habenular nucleus), it diminishes in size and no longer reaches the dorsal surface of the thalamus. It is still penetrated in its dorsal part by considerable numbers of fibres passing dorsally to the stria medullaris and as it appears to sink below the surface (when traced caudally) it remains for many sections apparently linked up with the stria by bundles of these fibres running dorsally to reach the

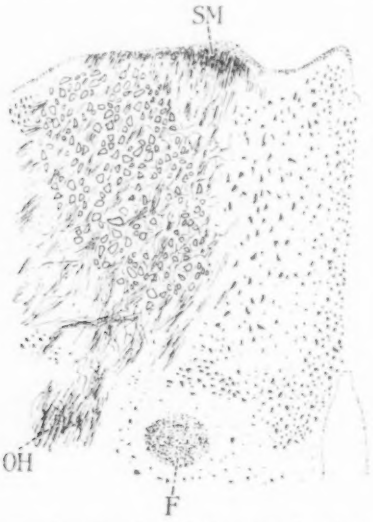

FIG. 5.—Tracing of a coronal section through the anterodorsal nucleus of *Macroscelides*. (× 42½.)

latter. The nucleus is here related laterally to the anterior end of the lateral nucleus and a fine plexus of medullated fibres extends across the line of junction from one nucleus to the other. Ventrally it is related to the commissura interanterodorsalis which is now better developed, and among the transversely running fibres are strewn the characteristic large angular cells derived from the anterodorsal nucleus and forming a commissural nucleus. By section 45, the anterodorsal nucleus has come to an end but the commissure still persists. While this commissure seems mainly to be composed of fibres that link up the anterodorsal nuclei of the two sides, it also receives fibres from the lateral

thalamic nucleus. Traces of this commissure with its large cells may be found caudally as far as section 70.

The *anteroventral element* of the anterior group of nuclei first appears in this series of transverse sections in section 21 as a group of small granular cells closely packed together and applied to the ventral pole of the anterodorsal nucleus. It is penetrated by discrete bundles of fibres derived from the lateral olfactohabenular tract and, more caudally, by fibres of the thalamic radiations. It takes on a triangular shape, being flattened on its dorsal aspect by apposition with the anterodorsal nucleus in front and to the commissure of this nucleus behind. It is quite sharply separated from the anteromedial element by a cell-free space and is further differentiated from this nucleus by the fact that its constituent cells are smaller, more closely packed, and somewhat more darkly stained. Further, unlike the anteromedial nucleus, it is freely penetrated by contributions from the inferior thalamic radiations. By section 70, the nucleus has disappeared. Throughout its extent, it does not extend further laterally than the lateral limit of the dorsal element and does not reach near the dorsal surface of the thalamus.

The *anteromedial nucleus* consists of larger cells which are angular and somewhat scattered. It appears rostrally in the same transverse plane as the anteroventral nucleus as a small group of cells situated to one side of the median plane. The nuclei of the two sides soon fuse together to form a broad band of cells stretching across the midline ventral to the *commissura interanterodorsalis* and dorsal to the nucleus reuniens. The nucleus is practically free of medullated fibres except caudally where they appear among the cells and pass ventrolaterally in a wavy course to join up with the bundle of Vicq d'Azyr. The nucleus finally disappears at about section 80.

The *mammillothalamic tract* can be followed to its termination particularly well in these sections. Traced dorsally (and anteriorly) the tract reaches the anterior nuclei at the lateral extremity of the anteromedial element towards its caudal limit. At this transverse level, it gives off contributions medially into the anteromedial element and to a lesser extent dorsolaterally into the anteroventral element. These fibres run in among the cells of these nuclei and become lost therein. A little more rostrally, a conspicuous bundle of fibres may be seen running from the tract dorsally into the commissure of the anterodorsal elements. These contributions to the commissure can be followed continuously in a rostral direction until the mammillothalamic tract itself finally reaches

the ventral aspect of the commissure (dorsal to the anteromedial and anteroventral nuclei) and disappears as a distinct bundle. The individual fibres passing to the commissure may in many cases be followed some distance. Most of them become lost in the intricate network of the commissure, some can be traced dorsolaterally, clearly aiming for the anterodorsal nucleus of the same side, while many turn medially in the commissure with the evident purpose of crossing the midline to reach the corresponding nucleus of the opposite side. The impression is gained that a large proportion of the fibres of Vicq d'Azyr's bundle thus terminate in connection with the anterodorsal nuclei of the same and opposite sides. A considerable number of fibres also terminate in the anteromedial nucleus, while relatively few reach the anteroventral element.

Erinaceus. (Figs. 5 and 6.)

Sections of the thalamus of this primitive insectivore give the impression that the cells of the thalamic nuclei are much more loosely packed than is the case with the other insectivora examined. As a consequence, the nuclei are more diffuse and not so clearly circumscribed. It is partly because of this fact that the identification of the elements of the anterior group of nuclei offers considerable difficulty. Indeed, without the study of the thalamus of *Macroscelides* as a link, it would hardly be possible by ordinary methods to make a certain comparison with the nuclei of the tree-shews.

The *anterodorsal nucleus* presents the greatest difficulty for identification. There is no circumscribed group of cells comparable with that found in the other forms, especially as it appears in *Macroscelides*. It may be said at once that if this element is represented in the hedgehog, it is extremely poorly defined and of insignificant size.

In the transverse series of sections there appears rostrally among the olfactohabenular fibres as they are approaching the dorsal surface of the thalamus a few scattered cells of angular and sub-angular shape, larger than the cells in most parts of the thalamus (with the exception of those forming the dorsomedial nucleus), and with cytoplasm staining rather more deeply than is the case with the cells of neighbouring nuclei. They lie in a matrix which stains a little darker with methylene blue than surrounding areas and which in iron-haemotoxylin sections is seen to be richly permeated with fine medullated fibres. The cells form a loosely packed group of oval form with its long axis directed vertically.

It lies medial to the main mass of fibres of the lateral olfactohabenular tract and dorsolateral to the anterior end of the nucleus reuniens. The group reaches a size shown in fig. 5a and then rapidly diminishes caudally. Its caudal extremity in transverse sections cannot be defined for it seems to be connected by a scattered band of cells with the anterior extremity of the dorsomedial nucleus of the thalamus. In sagittal sections, this group can be identified (fig. 6) lying anterodorsally to the small-celled anteroventral nucleus, in among the fibres which are passing up to form the stria medullaris. In these sections also it can be seen to be linked up with the anterior extremity of the dorsomedial

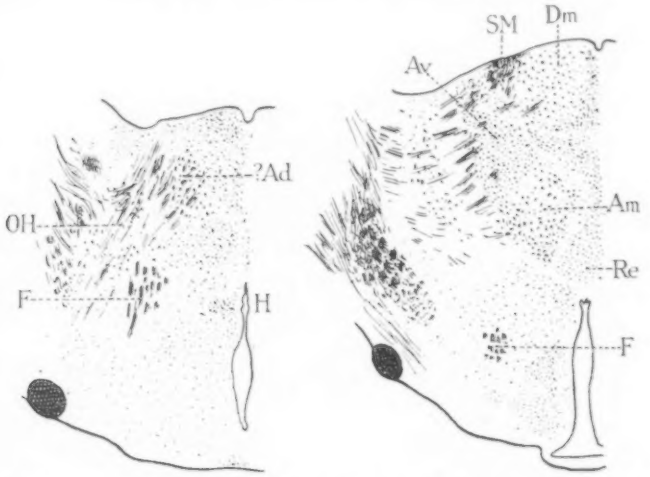

FIG. 6.—Coronal sections (5 and 16) of the thalamus of *Erinaceus*. (× 10½.)

nucleus by scattered and smaller cells. In the absence of any alternative interpretation, this group of cells may be provisionally regarded as representing the anterodorsal nucleus in *Erinaceus* because of the following characters: (1) Position. It may be pointed out, in this connection, that the cells lie in a relatively more anteroventral position than the anterodorsal nucleus of the other forms, and, moreover, in a position where Cajal's nucleus of the stria medullaris might be expected to lie. But the cells of the latter nucleus are typically very small and the position of the other anterior nuclear elements in *Erinaceus* differs from the condition in the other insectivora. (2) Relative size and staining properties of cells. (3) The group is permeated by fibres of the lateral olfactohabenular tract. (4) The cells lie in a matrix of fine

interlacing medullated fibres. In these features, this group of cells resembles the anterodorsal nucleus in other mammals. In any case, however, the small size and poorly defined nature of this group of cells should be emphasized. No interanterodorsal commissure could be recognized.

The *anteroventral nucleus*, although of irregular shape, can be identified by the small size of its constituent cells. Its general disposition corresponds to the same element in *Macroscelides* though it is much larger in extent. Immediately caudal to the plane at which the group labelled the anterodorsal nucleus ceases to be recognizable as a definite entity there appears a group of small triangular and rounded

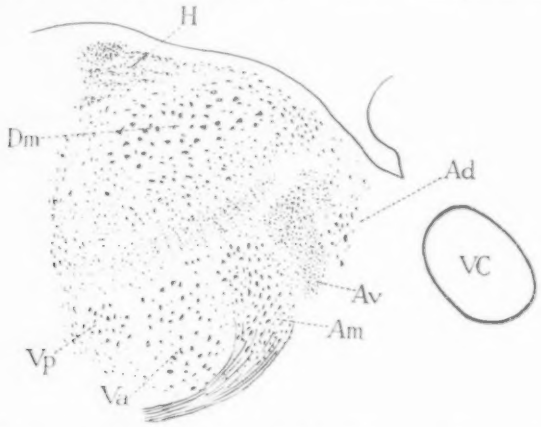

FIG. 7.—Sagittal section of the dorsal part of the thalamus of *Erinaceus*, close to the midline. The position of the mammillothalamic tract has been superimposed from the adjacent section stained with iron-haemotoxylin. (× 16.)

cells which are relatively closely packed together. It is related dorsally to the anterior end of the dorsomedial nucleus, laterally to the reticular nucleus and internal capsule, and medioventrally to the anteromedial nucleus and the nucleus reuniens. In its most rostral plane this small-celled group, the anteroventral nucleus, is irregularly circular in transverse section, but it rapidly assumes a triangular shape with its apex directed dorsolaterally towards the dorsal surface of the thalamus and its base ventromedially where it abuts against the anteromedial element. It is penetrated by compact bundles of fibres from the thalamic radiations which give to it a coarsely reticulated appearance in methylene blue sections. In its maximum extent, the nucleus extends dorsally between the nucleus reticulatus and the nucleus dorsomedialis

to reach the dorsal surface of the thalamus. More caudally, it recedes from the dorsal surface, being replaced by the anterior end of the lateral thalamic nucleus, and then gradually diminishes in size as it is traced backwards until it disappears. In sagittal sections, this nucleus is also clearly defined, lying anterodorsally to the anteromedial element, its more dorsal part being penetrated by fibres of the olfactohabenular tract.

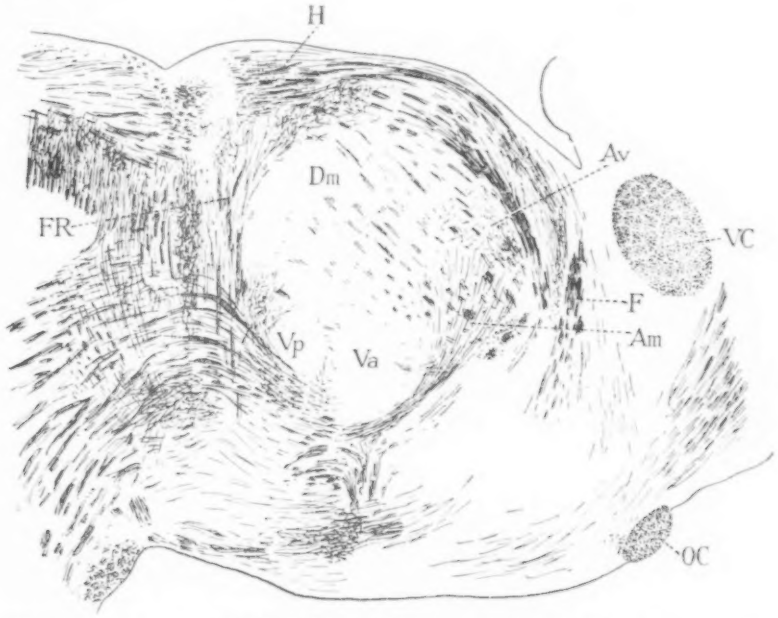

FIG. 8.—Sagittal section of the thalamus of *Erinaceus*, showing the fibre tracts. (× 16.)

The *anteromedial nucleus* makes its appearance at about the same transverse level as the anteroventral element. Its cells are larger than those of the latter, more scattered in their arrangement, and triangular or polygonal in shape. Rostrally it forms an oblique band of cells interposed between the anteroventral nucleus and the nucleus reuniens, and directed dorsomedially towards the median raphe where it appears to be linked up with the nucleus of the opposite side by similar cells extending across the midline. The caudal extremity of this nucleus is extremely difficult to define in transverse sections, for it seems to pass insensibly into the ventral nuclei of the thalamus. In sagittal sections, however, the distinction is clearer. Here the cells of the anteromedial

nucleus tend to be arranged in irregular rows and to lie with their long axes parallel to the brush-like termination of the fibres of the mammillothalamic tract. It is seen also that the cells are more closely packed together, and are a little smaller in general than those of the ventral nuclei. Moreover, in iron-hæmotoxylin sections, the nucleus is clearly defined by the fibres of the mammillothalamic tract.

The *mammillothalamic tract* (fig. 8), compared for instance with *Tupaia*, is much shorter and runs a more oblique course. At its upper extremity, it breaks up into a brush of fine fibres which run throughout the anteromedial nucleus. Many of these fine fibres can be traced to the dorsal aspect of the nucleus and it is certain that they pass on to make connection with the anteroventral element, even though such fibres could not be traced individually in continuity as far as this.

DISCUSSION.

It has been shown that three elements of the anterior group of nuclei can usually be recognized in the thalamus, but that these elements, even within the limits of the insectivora, show a great degree of variation in their relative size and differentiation, and in the characters of their constituent cells. It would be hardly possible, for instance, to make a comparison between the anterior nuclei of *Tupaia* and *Erinaceus* without noting their relation to the terminal fibres of the mammillothalamic tract and without the study of the thalamus of *Macroscelides* as in some way an intermediate link.

In the tree-shrews, the appearance of the anterior nuclei resembles that found in most mammals of a more specialized or advanced type. In *Macroscelides* an unusual condition is found which parallels the unusual features found in the brain of this animal generally. In *Erinaceus*, the interpretation, at first sight, is not easy. Judging from figures of the thalamus of the opossum given by Tsai [21], the anterior nuclei in this primitive animal closely resembles the condition found in the hedgehog. Moreover, the anterior nuclei of the hedgehog bear a much closer resemblance to the nuclear groups of the reptilian thalamus which have been regarded as equivalent to the anterior nuclei of mammals than is the case with the other insectivores. This is in accord with the general primitive features of the brain of *Erinaceus*.

It will be convenient to discuss separately the three anterior nuclei. The anterodorsal nucleus lies close to the dorsal surface of the thalamus in among the fibres of the olfactohabenular tract streaming up to

contribute to the stria medullaris. The constituent cells lie in a meshwork of fine medullated fibres, and are characterized by their deeply staining cytoplasm and their closely packed arrangement. When the nucleus is well developed, the cells are conspicuous for their large size. As regards the fibre connections of the anterodorsal nucleus, Cajal [4] found in his rodent material that fibres of the mammillothalamic tract reach it after having penetrated the anteroventral nucleus. This observation does not seem to have been corroborated by other authorities who have paid attention to this point. Thus Gurdjian, in his studies on the thalamus of the albino rat, could find no direct connection between the anterodorsal nucleus and the bundle of Vicq d'Azyr. In *Macroscelides*, however, where this nucleus is very conspicuously developed, the connection is obvious enough and such cases lead one to suppose that in those animals where the nucleus is relatively smaller the connection is also present although it may not be detected by ordinary histological methods. Laterally the anterodorsal nucleus is in intimate relation with the superior thalamic radiations, but the significance of these fibre connections of the anterior nuclei will be discussed below with the anteroventral nucleus. Kappers [12] believes that they are partly striatal and partly cortical in their termination, and that the thalamo-cortical fibres of the anterior group of nuclei probably arise from the dorsal element (Monakow's n. anterior C). He quotes Rutishauser's [18] observation that this element is found much degenerated after experimental lesions of the frontal region of the cerebral cortex. The close and constant relation which the anterodorsal nucleus always bears to the stria medullaris suggests the possibility of a functional relation. The sections of *Macroscelides* brain, indeed, do seem to indicate a direct fibre connection between the intercellular network of fibres in the anterodorsal nucleus and the stria medullaris, though a decisive statement cannot be made upon this point. Kappers observes that this nucleus lies apparently interpolated in the course of the tænia and that it seems to belong to this fibre tract. Papez [17] states definitely that in the cat his dorsomedial nucleus (= n. anterodorsalis) receives fibres from the olfactohabenular tract. On the other hand, Cajal emphatically remarks that while the nucleus (his angular nucleus) is traversed by fibres passing to the stria medullaris, these fibres all pass through it without interruption. This is clearly a matter which requires further investigation.

It has been shown that the anterodorsal nucleus attains a remarkable development in *Macroscelides*. In this, it parallels and surpasses the

condition which seems to be especially characteristic of the rodents as a group. In this connection it is relevant to note that the brain of *Macroscelides* shows many other resemblances to that of rodents, and especially in the strong development of the subsplenial portion of the hippocampus and the relatively great extent of the retrosplenial and associated cortical areas. In discussing the termination of the thalamo-cortical fibres which he believes are connected with the anterior nuclei,

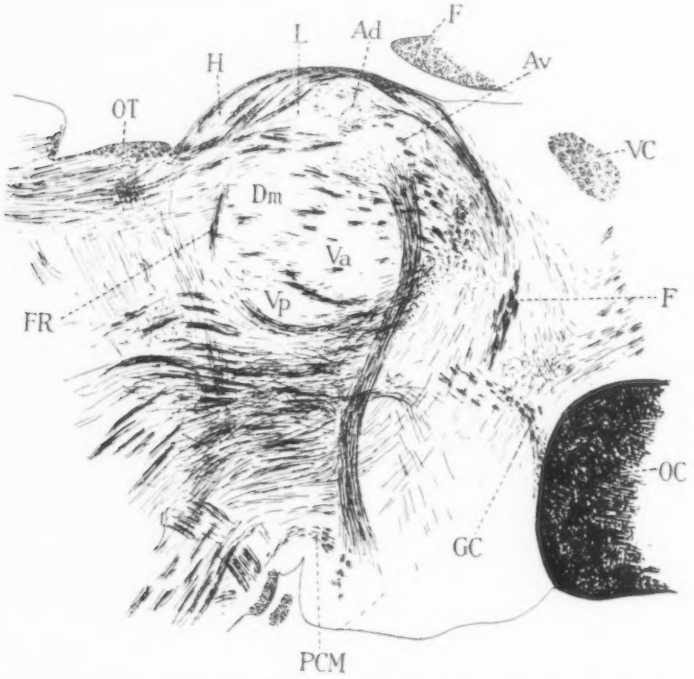

FIG. 9.—Sagittal section of the thalamus of *Tupaia minor*, showing the fibre tracts. The position of the lower end of the mammillothalamic tract has been traced in from an adjacent section in order to show the whole course of this tract. (× 16.)

Kappers states that it is not certainly decided whether these pass to the frontal lobes or to the regio cingularis or retrosplenialis of the cortex. The latter suggestion would seem to derive some support from the condition in the brains of rodents and especially *Macroscelides*, where an inordinate development of the anterodorsal nucleus is associated with an unusual development of the retrosplenial and cingular areas of the cortex cerebri [1, 7]. That the development of this nucleus is not

directly related to the primary and secondary olfactory centres is indicated by the fact that in *Erinaceus* it does not exist, at least as a clearly-defined group of cells. Such an example also indicates that a well-developed anterodorsal nucleus is not to be regarded as a primitive mammalian characteristic as has been done by some authors. Furthermore, the condition in the very primitive brain of *Erinaceus*, together with the absence of any element in the reptilian thalamus which can be directly compared with the anterodorsal nucleus, leads to the conclusion that the development of this nucleus is a mammalian character which becomes specialized in certain mammalian groups such as the rodents and the Macroscelididæ.

In *Ptilocercus*, the anterodorsal nucleus is, in relation to the anteroventral nucleus, much smaller than in *Macroscelides*, and its constituent cells are not nearly so large. In *Tupaia*, the nucleus is distinctly smaller than in *Ptilocercus*, and its cells are not in general larger than those of the other anterior nuclei. In this insectivore a condition has been reached which, indeed, approaches that characteristic of the Primates. In the latter group, the nucleus, if traced through different representatives from the lowest to the highest, shows a progressive tendency towards shrinkage and disappearance. These comparative observations have led to fallacious conclusions regarding the relation of the development of the nucleus to that of the olfactory regions of the brain. It may be noted, in this regard, that in *Tarsius*, in which the olfactory bulb and associated centres show a marked reduction, the anterodorsal nucleus is quite conspicuous.

The anteroventral nucleus is the element which forms such a conspicuous spherical and well-defined nucleus in the brains of most mammals, and which is often referred to as the anterior nucleus, the nucleus dorsalis, or the nucleus dorsalis magnus. It is commonly regarded as the main site of termination of the bundle of Vicq d'Azyr, but this is by no means necessarily so. The proportion of the fibres of the mammillothalamic tract which end in this nucleus depends upon the size of the nucleus relative to the other anterior nuclei. Thus, for instance, in the rat in which the anteromedial nucleus is relatively well developed, Gurdjian found that most of the fibres terminated in the latter nucleus and only a comparatively small proportion in the anteroventral nucleus. In *Macroscelides*, again, where the anterodorsal nucleus is so large, the majority of the fibres of the mammillothalamic tract end here. Abundant efferent fibres pass out from the lateral aspect of the anteroventral nucleus into the superior thalamic radiations. The ques-

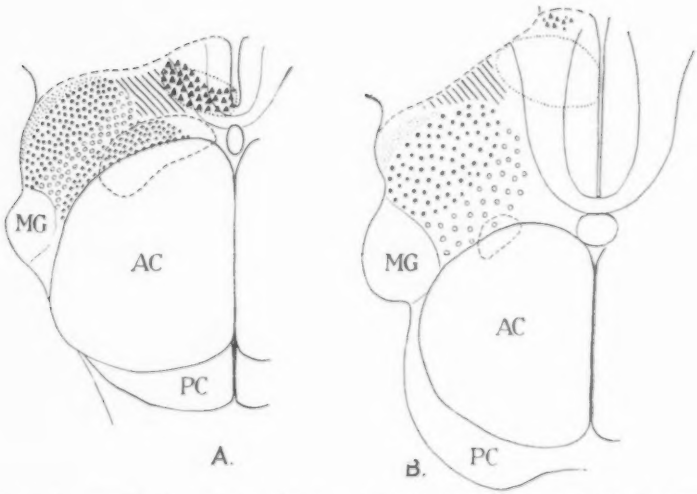

FIG. 10.—Dorsal view of the thalamus of (*a*) *Macroscelides* and (*b*) *Erinaceus* reconstructed from the coronal sections. In this and the next figure, some of the thalamic nuclei have been projected on to the dorsal surface of the thalamus. (× 8.) Black triangles = anterodorsal nucleus. Dotted line = anteroventral and anteromedial nuclei. Oblique lines = anterior part of the lateral nucleus. Fine dots = ventral nucleus of lateral geniculate body. Coarse dots = dorsal nucleus of lateral geniculate body. Circles = pars posterior of lateral nucleus. Crosses = pretectal nucleus. Interrupted line = posterior nucleus.

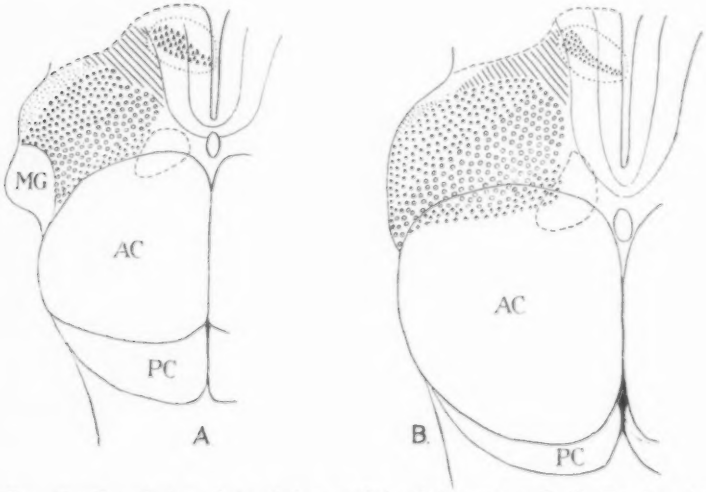

FIG. 11.—Dorsal view of the thalamus of (*a*) *Ptilocercus* and (*b*) *Tupaia minor*, reconstructed from the coronal sections. Nuclei indicated as in the previous figure. (× 8.)

tion as to whether these fibres terminate in the cortex or whether they only reach the striatum raises the interesting problem of a possible cortical connection of the anterior nucleus as a whole. As long ago as 1895, Monakow [15] adduced experimental and clinical evidence to suggest such a connection with the upper frontal convolutions or with the suprasplenial portion of the gyrus fornicatus. Lindon Mellus [14] found degenerated fibres passing to the anterior nucleus of the thalamus after experimental lesions in the frontal lobe of the monkey's brain. Similar findings by Rütishauser have been referred to above. Livini described fibres connecting the anterior nucleus with the gyrus fornicatus in *Hypsiprimnus*, and Sachs [19] accepts the possibility of such a connection in his comparative study of the mammalian thalamus. In another publication [20] dealing with an experimental study of the thalamus, however, the latter author denies the existence of any fibres passing direct from the anterior nucleus to the cortex, and states that these fibres terminate in the striatum. It should be noted that Sachs refers only to the anteroventral nucleus (his n. dorsalis magnus) and in this particular reference does not include a discussion of the anterodorsal element (his n. disseminatus). Cajal states definitely that the efferent fibres of his dorsal nucleus penetrate the corpus striatum and thus constitute an important thalamo-cortical fibre system. Kappers [12] sums up the evidence by expressing his belief that the anterior nucleus does give off cortical projection fibres. He deems it probable that these cortical fibres arise in the anterodorsal nucleus, while the main nucleus, the anteroventral nucleus, gives off most of the striatal fibres. In harmony with this idea is the fact that, as pointed out above, there appears to be no representative of the anterodorsal element in the reptilian brain in which a neopallium is hardly developed except possibly as a very primordial and elementary structure.

In *Erinaceus* and *Macroscelides*, the anteroventral nucleus has not the characteristic circular form, nor is it clearly defined by a capsule of medullated fibres as it is in most mammalian brains. It is rather of an irregular triangular shape extending dorsolaterally and, in the case of *Erinaceus*, reaching to the dorsal surface of the thalamus. It is relatively small in *Macroscelides*, but occupies a large area of the frontal part of the thalamus in *Erinaceus*. In the latter insectivore, the nucleus has a striking general appearance to the nucleus dorsolateralis anterior of the reptilian thalamus described by Huber and Crossby [11], and by Cairney [3]. This nucleus forms the lateral part of the cell-group in the reptilian thalamus described by De Lange [13] and Kappers as the

anterior nucleus. According to De Lange, there is in *Draco volans* a definite mammillothalamic tract terminating in this nucleus. Plentiful striothalamic connections between the nucleus dorsolateralis anterior of reptiles and the striatal regions of the forebrain by the lateral forebrain bundle have been described by various authors. Huber and Crossby conclude that one may regard the nucleus as the anlage of the portion of the nucleus anterior of mammals which has connections with the frontal cortical areas, or the somatic part of the anterior nucleus. A comparison with the thalamus of *Erinaceus* would appear to indicate that the n. dorsolateralis anterior is equivalent to the anteroventral nucleus of mammals, the thalamostriatal connections of which are certain, while, as is suggested above, it is the anterodorsal nucleus which is related to the cortex.

In the *Tupaiidæ*, the anteroventral nucleus is of a well-defined spherical form as in the brains of the higher mammals generally. It is somewhat smaller relatively in *Tupaia minor* than in *Ptilocercus*. This difference might be associated with the relative development of the olfactory centres of the brain in the two animals, but a survey of the brains of a large number of mammals shows no direct relation between the size of the anteroventral nucleus and the olfactory centres. In Primates, for instance, and even in Man, the anteroventral nucleus is well developed and remarkably differentiated, although the primary and secondary olfactory centres are much reduced.

The anteromedial nucleus is the least well defined of the anterior nuclei, and by many authors it has been dissociated from the anterior group of nuclei and included in the medial group. But its relation to the terminals of the mammillothalamic tract indicate its true position among the thalamic nuclei. It has already been pointed out that Gurdjian found most of the fibres of this tract terminating in this nucleus in the rat. In *Erinaceus*, the same condition is found, the termination of the tract being much more closely related to the anteromedial than to the anteroventral nucleus. It is doubtful whether this element is related to the fibres of the thalamic radiations as are the other elements of the anterior nucleus. Gurdjian states that the anteromedial nucleus in the rat receives "but very few fibres (if any at all) from this system." Our observations on the same nucleus in the insectivora point to the same conclusion. It is probable, indeed, that this nucleus belongs to the palæothalamus and is only in direct fibre connection with other thalamic nuclei and with the hypothalamus. A comparison with the primitive condition in the thalamus of *Erinaceus* suggests strongly that the

reptilian nucleus dorsomedialis anterior (of Huber and Crossby, and Cairney) is its homologue. It is this nucleus which appears to be in most direct relation with the mammillothalamic tract described by De Lange in reptiles. According to Cairney, also, in Sphenodon, it receives part of his fasciculus diencephalicus periventricularis which he intimates is the equivalent of De Lange's mammillothalamic tract. Moreover, the dorsomedial anterior nucleus of reptiles in contrast to the dorsolateral anterior nucleus is not connected to the striatum by thalamostriatal fibres, or only to a very insignificant extent.

While in most mammalian brains the cellular elements of the anteromedial nucleus do not differ to any marked extent from those of the anteroventral nucleus, in *Erinaceus*, and to a lesser extent in *Macroscelides*, the cell types are clearly distinct. In these insectivores, also, the anteromedial nucleus is large and well differentiated in comparison with the anteroventral nucleus. This is a feature to be anticipated in the most primitive mammalian brains in which the palæothalamic nuclei may be expected to be relatively more obtrusive. In higher forms, the nucleus is more diffuse and in no way clearly delimited in sections stained to display the cyto-architecture of the thalamus. It also undergoes a reduction in size in relation to the anteroventral element. We may say, then, that the comparative anatomical evidence favours the following interpretation of the significance of the anterior thalamic nuclei. These nuclei serve for the reception of impulses relayed on from the mammillary bodies. This part of the hypothalamus is primitively connected with the mid-brain and hind-brain by way of the mammillotegmental fibres, as well as with the archipallium by the fornix. In some reptiles there is evidence of a mammillothalamic tract which ascends to the anterior and dorsal part of the thalamus. This tract at first mainly terminates in the anteromedial nucleus (or its homologue) in reptiles and primitive mammals, and the anteromedial nucleus is to be regarded as a part of the palæothalamus and not primarily a somatic centre. The somatic part of the anterior group of nuclei is first represented by the anteroventral nucleus (or its reptilian equivalent) which relays on to the neostriatum. Finally a third element, the anterodorsal nucleus, which is not definitely recognizable in reptiles and the most primitive mammals, possibly serves as a relay station through which impulses derived from the mammillary region may be carried on to the cerebral cortex. This third element only reaches a marked development in certain specialized mammalian brains, such as the brains of the Macroscelididæ and (to a lesser extent) the rodents.

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THE SIGNIFICANCE OF SOME VARIATIONS IN THE KNEE-JERK IN DISEASES OF THE CENTRAL NERVOUS SYSTEM.[1]

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[1] From the Department of Neurology, University College Hospital, and the National Hospital, Queen Square. The expenses of this investigation were met by Grants from the Medical Research Council, and the Board of Management of the National Hospital.

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Introduction.

During the course of the year 1875 there appeared in the *Archives für Psychiatrie und Nervenkrankungen* two articles, one by Erb and the other by Westphal, both dealing with the knee-jerk. These appear to have been the first recorded studies of a phenomenon to which references can be traced in medical literature as far back as the last quarter of the eighteenth century and which had received current recognition in Charcot's clinic since 1862.

It is of interest to note that from their first approach to this subject these two observers differed upon one vital point in the interpretation of what occurred, and this was reflected in the title given by each to his paper—Erb describing the "Sehnenreflexe," and Westphal, with less avowed decision, "eine Bewegungserscheinung." This difference in interpretation persists to the present day, even after very many contributions have been made towards its settlement. Erb held that the knee-jerk and allied reflexes were true "reflexes" involving nervous paths; Westphal said that they were local muscle responses dependent upon peripheral excitability alone to which central nervous connections were purely adventitious.

The work devoted to the study of these reflexes and the articles written about them are difficult of enumeration. In 1893, only eighteen years later, Sternberg in his monograph quoted from over 300 articles written around the subject and from the published results of thirty-five different workers who had recorded graphically movements of the limbs elicited as tendon reflexes. Since that time, although the methods of recording and the clinical observations have multiplied very greatly, the important questions with which discussion has been concerned are few and they may be briefly summarized thus:—

(1) The occurrence of the knee-jerk and the conditions associated with its absence or exaggeration.

(2) The qualitative changes of form of this response found in persons

suffering from various diseases and the means of reproducing these changes experimentally.

(3) The nature of the phenomenon — a response to local muscle irritability or to a nervous reflex.

The observations and experiments upon which this paper is based have some bearing upon each of these questions, and the results of the method here introduced of recording muscular contractions are offered as a contribution to the subject as a whole.

The Clinical Significance of the Knee-jerk.

The prominent place which examination of the tendon response has held in the routine of neurological investigation is mainly due to the fact that the percussion hammer provides the clinician with a form of interrogation which forces from the nervous system a succinct answer, as Babinski [2] has phrased it. This answer is in the form of a clearly visible somatic change—a piece of objective evidence which if properly interpreted can throw light upon the integrity or impairment of definite and distinct parts of the nervous system. For its interpretation to be sound it must be systematized and correlated with the other relevant clinical and pathological evidence. Changes in this particular reflex associated with various conditions and lesions have been recorded as simple presence or absence of the reflex, its diminution or exaggeration and certain characteristic changes in form.

The attempt to explain these clinical observations in terms of physiological function is not confined to recent years, but it is only recently that physiology has been able to offer any acceptable explanation. Function in the physiological sense is inseparably bound up with the idea of purpose, but for the tendon reflexes no clearly satisfactory purpose can be claimed. Of earlier writers, Erb [18], de Watteville [92] and Mommsen [56] pronounced them to be purposeless with all the more alacrity because this accorded with their view that they were local, peripheral phenomena. Sternberg concluded that they were developed to provide a protection to the joints against sudden shock by acting as splints both to aid the ligament in keeping the joint surfaces in apposition and to prevent any extreme displacement of the limb segments; their exaggeration with the development of spasticity when the limb was completely paralysed for voluntary efforts, and the arthropathies which often resulted when they were lost as in tabes dorsalis, being adduced in confirmation of this view. Even if regarded in the light of recent work as particular examples of the stretch reflex, the

postural functions of which are readily acceptable, their mechanism is explained but still not their purpose. This view does, however, provide an explanation for certain clinical correlates of the tendon-jerks, muscle tone, clonus, &c., and helps to systematize many associated but otherwise unrelated clinical observations. These observations, which we have seen above to be concerned with certain changes in the reflexes, may now be considered in detail.

The Presence or Absence of the Knee-jerk.

In common with the other tendon reflexes the knee-jerks are notoriously difficult to elicit in infants, but their presence is so nearly universal in adults who in other respects at least show no signs of abormality, that they are usually regarded as constantly present. Of the clinicians who have recorded their failures to elicit the knee-jerk in such subjects the following list provides typical examples:—

Pelizaeus [63], in 2,403 children, 0 failures.

Sternberg [83], in 6,000 adults, 1 failure (in whom all tendon reflexes were lost).

Jendrassik [44], in 1,000 adults, 1 failure (a case of diabetes).

Zenner [96], in 1,000 adults, 2 failures.

Block [8] reports 0·72 per cent. failures.

Berger [7] reports 1·56 per cent. failures.

Eulenberg [19] reports 4·8 per cent. failures.

When it is remembered that certain conditions such as even a slight peripheral neuritis may abolish the tendon responses long after other signs have disappeared, much value cannot be attached to their loss as an isolated abnormality, and to state, as Hoffmann [36] has stated, that if "in normal patients" no tendon reflex can be elicited with the help of the usual facilitation manœuvres then "this is pathological," is meaningless.

The cases in which the absence of the knee-jerk is of known significance fall into two main groups—those in which it has shared a fate common to all the tendon reflexes of that person, and those in which its absence contrasts with the preservation of the other knee-jerk or of neighbouring reflexes such as the ankle-jerk. Examples of the former group are seen in the conditions of marasmus, weakness and encephalitis (Sternberg [83]), profound asphyxia and narcosis (Risien Russell [70]) and after epileptic fits (Beevor [6]), conditions all of general nervous inexcitability or exhaustion. Their absence, with preservation of the ankle-jerks, is of much more definite and localizing significance.

Westphal [95] himself pointed out that this occurred in cases of spinal lesion. Sternberg [83] quotes cases showing that this usually argues a local nuclear lesion involving the origin of the anterior roots of nerves which go to the quadriceps femoris, but he amplifies Westphal's observation that it may occur after some fevers, typhus, smallpox, &c., by adding to this list the terminal stages of many infective diseases and the recovery phase from an epileptic fit. The particular value of such loss when it is restricted to one knee-jerk lies in the evidence it gives for localizing the lesion in some part of the essential nervous connection of the muscle which fails to respond.

Qualitative Changes in the Knee-jerks.

Impairment of the knee-jerks has been recorded in muscular diseases affecting the quadriceps femoris, and in peripheral neuritis, tumours, &c., interrupting either its sensory or its motor connections.

Within the central nervous system the lesions which give impairment or exaggeration of the knee-jerks have gradually been localized in definite tracts or centres whose involvement may be expected to give characteristic changes in one or other of these directions. Thus a lesion of the pyramidal tracts in any part of their paths from the cortex to the lumbar cord leads eventually to exaggeration of the reflexes, whatever may be the much discussed mechanism providing this effect. Lesions of the cerebellum have frequently been claimed to provide an impairment of the knee-jerks, an unilateral lesion exercising this effect over the ipsilateral reflex (Jackson [40], Bastian [4], Bowlby [12], Fergusson [21], &c.), but it is doubtful if this is strictly true, as lesions rigidly limited to the cerebellum have frequently failed to show this effect.

That exaggeration of the knee jerks may be seen in neurotic and highly excitable subjects in the absence of organic lesions has always been recognized, and many attempts have been made to discriminate between the exaggerations due to this condition and those due to organic lesions. Lewandowsky [46] held that the addition of an adductor contraction to that in the quadriceps was definite evidence of organic disease, and Hoffmann [36] that maintained clonus was similarly conclusive. It is, however, generally recognised that neither of these provides an absolute criterion for the decision in question and no other is as yet forthcoming.

Apart from exaggeration and diminution, changes in form of the contraction have been described only in chorea and cerebellar disease—

the "sustained" jerk of the one and the "pendular" jerk of the other being well recognized.

Purpose of the Present Work.

The above clinical variations have been recognized as detectable in the knee-jerk as elicited at the bedside and it was considered possible that these might be explained and others revealed in graphic records of the actual reflex contraction. It was with this in view that the present work was undertaken. It was necessary before starting to determine what stimulus must be given and how it can be graded, what the response to this stimulus could be expected to be and how it could be recorded and also what were the extraneous factors or conditions which could modify the reflex. The necessary conditions of recording dictated by these considerations are summarized in the following paragraphs.

The Excitability of the Muscle.

All authorities are agreed that the muscle must be under some initial tension and that this tension must be partly active, i.e., no amount of passive stretch will produce the necessary tension background for a knee-jerk in the absence of all active contraction.

The presence of such a state of constant active contraction in the muscles of normal, healthy persons was suspected (Müller, Marshall Hall [54]), and even demonstrated in the frog (Brondgeest [10]) many years before the tendon reflexes were described, and although not mentioned by Erb (who, on the contrary, stated that the limb should be investigated so that all the muscles were slack) its importance is recognized by Westphal as an essential condition for the appearance of these reflexes.

All subsequent observers have given due recognition to its importance but their emphasis has varied according to the view which they took as to the reflex or local origin of the tendon-jerk. Those who favoured the local-response theory were at pains to explain the obvious dependence of the tendon-jerks upon connections with the central nervous system, and found in the necessary presence of some tonic innervation an explanation of this dependence which allowed them to maintain their view that the response was a local one—the local irritability being itself dependent upon maintained connection with the nervous axis, and kept up either by the tonic contraction itself or by some necessarily associated means (Eulenberg [19], Zielien [7], Waller [90], de Watteville [92], Beevor [6], Gowers [32], Ferrier [22], Horsley [39]).

As a result of his researches upon the reflexes of the lower limb, in particular upon ankle-clonus, Hoffmann [35] has recently pointed out that voluntary innervation can in some cases bring out a reflex contraction to stretch not otherwise present. He suggests that it may of itself be sufficient to provide the necessary background of active tension upon which the tendon-jerk can appear in the absence of any normal muscle tone. Attempts have been made in the present work to obtain a tendon response from flaccid limbs in which steady active tension has been meanwhile produced by either voluntary effort or faradism of the motor nerve, but all have failed. In the absence of any further evidence in support of Hoffmann's suggestion it may be asserted that some degree of tonic innervation is an essential factor in the production of a tendon reflex.

The many conditions of disease in which the degree of muscle tone and the facility of eliciting the reflexes obviously go hand in hand are too well known to need emphasis—more important are those cases in which there is a discrepancy between these two, because the adequacy of the "local response" hypothesis stands or falls by this relation. It has been claimed, for example, by Foerster [23], that in some nuclear lesions and in some cases of lateral column affection the tendon response may be absent while the tone of the muscle is normally present or even increased; that in others, e.g., high spinal lesions, incomplete transverse spinal lesions and cerebellar lesions, the tendon-jerks may be increased while the tone is diminished or not demonstrably present at all; and that in the recovery stage of a cortical paraplegia the tendon-jerks reappear and become facile before any tone becomes appreciable. Lombard [48] considers that voluntary "reinforcement efforts" give increase of the tendon reflexes without increase of tone and provide another example of the same lack of correspondence.

It is, moreover, clear that so long as a certain measure of resistance to passive movements is taken as evidence of a corresponding degree of muscle tone, such discrepancies are bound to show themselves. Variations in purely peripheral, mechanical resistance, defective voluntary relaxation and that type of rigidity which has come to be regarded as associated with extrapyramidal cerebrospinal innervations all vitiate an accurate assessment of true muscle tone by purely manual manipulation, and the common practice is not to take the degree of muscle tone as indicating the probable condition of the tendon reflexes but to regard the facility of these reflexes as giving the most trustworthy indication of the presence and degree of tonic innervation. From these considera-

tions it was clear that some means must be adopted for measuring the active and passive components of muscle tension.

The Nature and Site of the Stimulus.

From the earliest description of the reflex the most effective mechanical stimulus was described as a short, sharp blow. Both Erb and Westphal stress this, and it is given prominence in the first important résumé of the knowledge of such phenomena by Peticlerc [62], who insists upon "un coup sec." They state, however, that such a blow may be expected in normal cases to give rise to the typical reflex contraction when applied at a variety of places—to the muscle, its tendon, the knee-joint and certain parts of the leg, especially over the subcutaneous surface of the tibia. That a blow in any of these situations may elicit contraction of the quadriceps was not in dispute, it was a matter of common observation, but a sharp difference of opinion as to the mechanism whereby these stimuli acted at once arose and still persists.

The joint capsule had a short-lived reputation as a possible receptor of the stimulus. Jendrassik [44] and Schreiber both claimed to have obtained typical contractions in dogs from hitting the joint capsule after this had been completely freed from surrounding tissues. This result was never substantiated under conditions which precluded a purely mechanical spread of disturbance to the muscle connections, and the notion of such "joint reflexes" has not survived.

The claim of the periosteum as a receptor has many adherents and demands much more attention. The idea that the contraction following a blow over the subcutaneous surface of the tibia was set up by direct stimulation of the periosteum was already presented by Erb in his original article. It was subscribed to by Strümpell [80] upon no very adequate grounds and vigorously championed by Sternberg, who performed a series of careful and detailed experiments in which the piece of bone whose periosteal envelope was struck was isolated by resecting a section of bone proximally to it, so that it remained connected with the rest of the limb and with the central nervous system only through the medium of certain soft tissues not under tension. He found that a blow upon this periosteum elicited a contraction in the muscle registered, claiming from this that periosteal reflexes had an independent existence apart from any stretching response.

This result was not repeated by any of the observers under such

carefully controlled conditions, but those who deny to the periosteum any such rôle were many and emphatic in their scepticism.

Prevost and Waller [66], Gowers [32] and Hoffmann [35] held that stimuli applied over periosteum acted through a stretching of the muscle produced indirectly, either by a change in position of the bone struck or by a general transmitted vibration. Even the "radial periosteal reflex," allowed by all to occur, was said by Dumpert and Flick [17] to be absent when the fore-arm was supported, so that even slight extension of the elbow due to the blow was prevented. Yet as recently as 1927 we find Foerster [23] coming into the field as a staunch protagonist of the other view and supporting Sternberg in his contention. He claims that the last statement is incorrect: that, moreover, with regard to this particular reflex it can be elicited with the fore-arm in complete supination, so that the blow does not tend to extend the elbow, and also even from the ulnar border of the radius in some cases (paradoxical triceps reflex) in which the biceps, which contracts, has been directly slackened by the stimulus. He supports his view by adducing as further evidence the facts that in spastic cases a blow over one bony prominence will give rise to contractions in a whole series of muscles, some of which at least must have been slackened and not stretched as a result, and that in another case, one of hemiplegia, in which he had de-afferented certain muscles on the afflicted side, a blow to the bone of the sound leg caused a widespread contraction of muscles on the hemiplegic side, some of which were de-afferented and cannot therefore have contracted in response to stretch.

But these arguments do not bear criticism.

It has not been established that the reflex muscular contraction is always limited strictly to the muscle stretched in those cases in which the stimulus provided nothing but stretch and no excitation of periosteum. Therefore when a limb is vibrated or moved in any way owing to a blow upon some periosteum, it cannot be reasonably asserted that the stretching thereby provided is not of itself sufficient to set up contraction in all those other muscles in which it is in fact observed, i.e., that there must be some other source of irradiated reflex. When the knee-jerk of a spastic patient is taken in the usual way, the adductor jerks which are so frequently seen may be due to movements which are transmitted via the pelvis, as stretch, to those muscles. But there is ample evidence (Bohme [9]) to support the view that the reflex set up by tapping the patellar tendon and stretching the quadriceps femoris spreads in the central nervous system to give contraction of these muscles and probably

of others. Such a view accounts also for the occurrence of a paradoxical triceps reflex.

This is found predominantly in the cases of a nuclear lesion of the triceps innervation, and all of its appearances may be explained either on the grounds of irradiation within the central nervous system, the nuclear lesion preventing activation of the triceps, or in that the reflex setting (Schaltung) of the cord at the moment of stimulation is such as to favour reflex activation of the flexors rather than that of the extensors.

Foerster's argument from the case of hemiplegia in particular will not bear scrutiny, for Sherrington has shown that the possible contralateral reflexes which may be set up even by such a well-defined stimulus as electrical excitation of an afferent nerve-trunk, are so interchangeable that nothing may be deduced from the contralateral response to hitting some bony prominence of the limb.

We may conclude as a result of this, that it has not been shown that the periosteal reflex plays any part in producing contraction of the quadriceps femoris, and that the observations which were put forward in its support can be adequately explained in another way more in line with the other phenomena studied.

There remains for consideration the effect of the stimulus upon the muscle complex, i.e., the muscle with the patella and its tendon.

It is by a blow over the tendon that the reflex is commonly initiated; such a blow may be effective through stimulation of the overlying skin, of the tendon itself or of the muscles to which it is attached. Although Erb has shown that when the skin was picked up and struck no contraction resulted, Jendrassik [44] claimed to have elicited one in response to painful non-mechanical irritation of the skin, a contraction which, however, came on after a longer latent period and which he called a "pseudo-knee reflex."

The presence of nerves in the patellar tendon was first demonstrated by Sachs [73], although Rollet [71] had previously described them in that of the sterno-cutaneous muscle of the frog and obtained no contraction in response to their direct electrical stimulation. It was Tchirjew [84] who showed that the function of the tendon as an elastic connection between muscle and bone was sufficient to explain the effects of striking it, for contraction of the quadriceps resulted when the tendon, denervated by isolating it from skin and bone and crushing its line of connection with the muscle, was then stretched and struck. Schreiber completed the argument by substituting for the tendon a string tied to

the lower end of the muscle without impairing in any way the response. Gowers [32] and Schultze [81] had both come to the same conclusion from their study of the tendo Achillis jerk. Jendrassik [44] and Rosenheim [72] were the sole dissentients from this view. The former claimed that a typical reflex could be elicited when the freed tendon attached to the slackened muscle was supported upon a board and hit. Rosenheim came somewhat prematurely to the conclusion that the whole tendon phenomena were not reflex because he claimed to have obtained similar contractions from electrical stimulation of the freed patellar tendon. Sternberg repeated the experiment of Jendrassik but failed to confirm the results.

Gowers appears to have been the first to point out that a blow upon the upper edge of the patella could elicit the typical contraction although with less ease than one on the tendon. That in certain cases a blow over the belly of the stretched muscle set up a response was also shown by Sternberg.

The immediate result common to effective stimulation at all these various sites was a sudden lengthening of the already stretched muscle, and holding this to be the adequate and necessary stimulus to contraction Gowers referred to the phenomenon as a myotatic reflex.

The Receptors of the Stimulus.

Since some initial tension in the muscle is essential for the response, it is impossible to determine whether normally the adequate stimulus is a sudden increase in length or one in tension.

It has comparatively recently been decided that of the various forms of nerve end-organ in the muscle, it is the Golgi tendon organ which initiates an afferent stimulus in response to sudden stretch or increase in tension. Hinsey [34] has shown these to be always associated with muscle fibres and not to exist in the tendon. With a muscle in a normal degree of tonic innervation these tendon organs are all constantly supplying afferent stimuli to the nervous system (Adrian [1])—the effect of the sudden stretch of the whole muscle produced via its tendon is to cause these to fire off maximally and synchronously—providing in normal cases sudden discharge of the motor neurones innervating the muscle in which they are situated ; or in abnormal cases a series of such discharges not limited to the original muscle.

If the intramuscular receptors are paralysed by novocain, no reflex contraction to stretching can be elicited, and Foerster holds that the loss of the tendon reflexes in severe tabes dorsalis is in part at least due

to anæsthesia of these receptors; for Mann and Schleier [51] have shown that in such cases stretching of the muscle produces no electrical response in the posterior roots.

It seemed, therefore, clear from a consideration of the nature and of the receptors of the stimulus that, provided some means were adopted of giving a sudden sharp stretch to the muscle itself, nothing else was achieved by percussing in any particular place, and that the amount and rapidity of this stretch determined a complete evaluation of the stimulus.

The Course of the Contraction.

With increasing vigour of the knee-jerk there may be observed a gradation of the response commencing with a just palpable thickening of the vastus internus muscle, and, passing through various degrees of visible thickening of the whole quadriceps femoris, until a stage is reached in which shortening of the muscle with extension of the knee and a kick-up of the pendent foot is observed. As the strength of the response increases still further, the contraction spreads to other muscles, first ipsilateral and then crossed, the adductors being those which most frequently contract.

This irradiation of the response was not at first regarded as genuine—it was explained as being due to an irradiation of the stimulus through skeletal vibrations. Waller [90] found that the crossed adductor contraction in a rabbit was abolished after the femur of the stimulated limb had been broken across. Many others agreed that the widespread contractions were all parts of the response to the stretch of one muscle, and even used this view, while still a hypothesis, to substantiate their claim that the phenomenon in the particular muscle stretched must be reflex and not merely local (Hombrand, Dodge [16]). Most of the recent work (Hoffmann [35], Warder, Sherrington) supports the view that the impulses may spread in the central nervous system over neighbouring neurones and innervate them reflexly.

In the present observation it was decided to limit the recording of the response to that shown in the quadriceps femoris muscle, both because a particularly favourable means was found of leading off simultaneously from all the component parts of this through its tendon, and because it was the only muscle of which the tension could be accurately recorded. It was, however, recognized that contraction of the quadriceps alone was in some cases probably only a part of the total response.

The Anatomical Mechanism.

Experiment and observation have together defined certain nervous connections of the muscle as being both necessary and sufficient for the establishment of the reflex. These comprise the receptors in the muscle itself, afferent and efferent components and certain parts of the central nervous axis.

The nature of the receptors has been dealt with in another section of this paper, but it may be pointed out here that Magnus and Liljestrand [52] have shown that the reflex can be abolished by cocainizing the muscle in such a way that its motor power to other forms of stimulus is undiminished, i.e., the receptors alone are affected. The fact that there is complete unanimity with regard to the other parts of the reflex arc makes their enumeration simple. The afferent impulses leave and the efferent impulses reach the muscle along the same nerve—the anterior crural. Sherrington has shown that in the cat the afferent fibres enter the cord through the third and fourth lumbar posterior roots, and that the efferent fibres emerge from the anterior horns of the fourth and fifth lumbar segments. The brevity of the latent period led workers (Hoffmann [35], Jolly [45]) on this subject very early to suggest that there are no intercalated neurones between these two sets of fibres, and later the estimation of the proportions of this delay which may be attributed to conduction within the cord supported their view; but the more recent work of Sherrington and his co-workers seems to indicate that some, at least, of the phenomena of these reflexes are more easily explained on the assumption that there are, at least, two synapses upon this part of the path.

The functional interruption of any of the paths above detailed is alone sufficient to abolish the reflex, as is also destruction of the corresponding segments of the cord. The reflexes persist in rabbits after total destruction of the cord two segments above this level (Waller [90]), so that it is clear that this mechanism is sufficient in itself to provide the reflex. Although no one has questioned this sufficiently it has been suggested that other higher centres may sometimes collaborate. Wertheim Salomonson [94] claims to have found evidence for a component of the reflex involving a centre in the brain in much the same way as Sherrington implicated a pre-spinal centre anterior to the pons in the production of a crossed extensor thrust in which the same muscle plays a predominant part. Whatever rôle such additions to the simple reflex arc may have, all are agreed that they are accessory and subordinate.

It is interesting in this morphological context to note that Waller observed, without explaining it, the fact that seventeen months after cutting the anterior crural nerve in a rabbit regeneration was complete, the tone and the voluntary innervation of the muscle appeared faultless, and yet the knee-jerk had not reappeared. Sherrington demonstrated that the reflex could be abolished not only by severing the posterior roots traversed by the afferent impulses but by merely diminishing their conductivity. Both of these observations are associated with one well known to the clinician, that with impairment of peripheral conduction, as in a neuritis, the tendon responses are early, and sometimes permanently, abolished, thus making them especially sensitive indicators of slight peripheral nerve damage.

The Nature of Modifying Influences.

The association between tonic innervation of a muscle and its tendon reflex is so close that any apparent departure from this excites comment. That this tone is maintained reflexly through the central nervous system is universally allowed. The cases in which the tendon-jerk is present while muscle tone seems absent are not sufficiently well established to allow of their being used as conclusive evidence that the nervous connections are essential apart from the provision of tone.

The modification which the reflex undergoes with different changes in distant parts of the central nervous system, gross pathological lesions, cortical activity, &c., lends colour to the reflex theory in that most of these changes cannot be supposed to produce their effect outside the cerebrospinal axis itself.

It was frequently held by earlier observers that inhibition of the knee-jerk did not take place; de Watteville stated this and Erb had previously concluded that it could not be inhibited but only antagonized. Sherrington, however, clearly demonstrated the possibility of inhibition (*Proc. Roy. Soc.*, B 52), in 1892.

The phenomenon of reinforcement appears to have passed without dispute, although various untenable theories were put forward to explain its mechanism. Since its first description by Jendrassik [43] many authorities, including Mitchell and Lewis [55], Lombard [49], Bowditch and Warren [11], have investigated the conditions of its occurrence.

The question as to whether voluntary reinforcement efforts, when performed alone, give any shortening or increase of tone in the quadriceps has been variously answered by different authors. Lombard held that they did not; Golla [29] claims to have demonstrated shortening of

the passively extended muscle brought about by either muscular or mental effort, and holds further that the increase in tone is proportional to the effort put forth ; Lombard could find no increase in the excitability of the muscle to electrical stimulation during voluntary mechanical effort, so that there is no adequate explanation of reinforcement in terms of purely peripheral changes. Most authors attempt to bring its influence into line with the established fact that interruption of cortico-spinal paths above the lumbar segments leads to exaggeration of the knee-jerks, by assuming that some normally constant degree of innervation down these paths provides a steady level of inhibition over the local reflex centre, and that as a consequence of voluntary effort the essentially single-minded cerebrum becomes in some vague way preoccupied so that this inhibitory stream diminishes.

On the other hand a directly opposite view of the mechanism of reinforcement has been put forward by Hoffmann [36], Nonne [60], Karger and others. Hoffmann claims that the pyramidal tract carries facilitating stimuli, because with maximal voluntary relaxation the current of action of the tendon response is diminished, and with voluntary contraction of the muscle it is increased (see also Wacholder and Altenburger [89]), and the refractory period of the response is lessened. When the muscle is in voluntary contraction, he argues, although we may not be able to see the knee-jerk the fact that one actually supervenes upon an appropriate stimulus is clearly shown by the typical action current which follows, even when the quadriceps is being contracted powerfully against a resistance. He concludes, therefore, that during voluntary reinforcement efforts there is in some way an indiscriminate overflow of cortical activity increasing amongst other things this flow of facilitating impulses. Nonne [60] supports this view with the claim that in hysterical hemiplegia there is often a loss of tendon responses on the afflicted side, and that these appear when the condition clears up and voluntary movements return. Karger's contribution is the observation that during sleep and other states of diminished general innervation the knee-jerk is found to be absent.

V. Weizsacker [93], realizing no doubt the imperfect character of the explanations afforded by either of the above theories alone, came to the conclusion that the Jendrassik "Handgriff" acts either by making the muscle slack from inattention or by giving a slack muscle some "Mitinnervation," a conclusion which does not considerably further our understanding of the problem.

There are certain other indirect modifying influences to which the

response is subject. The action of narcotics has been investigated by clinicians and experimental workers. Erb held that the response was uninfluenced by drugs; Horsley [39] pointed out that they survived the administration of nitrous oxide in anæsthetic doses after the cutaneous response had disappeared. Reinhard [69] found them abolished in deep chloroform anæsthesia, an observation confirmed by Eulenberg [19], who maintained that they were not similarly affected by ether. Asphyxial states abolished them (Eulenberg [19], Reinhard [69]), as did also coma (Sternberg [83]) from whatever cause. After sudden death a diminution in the reflex can be seen in one minute and it is rare for any response to survive for more than forty minutes. The knee-jerks, which persist indefinitely upon repeated stimulation when the subject is at rest and unfatigued, may disappear when a condition of general exhaustion follows strenuous over-activity (Dodge [16], Oekonomakis [61], Schenk and Wissemann [79], Brissaud [13], Marinian [53]). Allied with this disappearance is their absence after an epileptic fit (Beevor [6]) and in febrile conditions, especially in children (Bohme [9]). Other general influencing factors have been commented upon, such as the increase in the reflex on cooling by a cold bath (Beevor [6], Sternberg), or the simultaneous application of non-localized electrical stimuli to the limb (Sternberg, Levandowsky [46], Neuhof [59]).

This review of the different factors which are known to modify the knee-jerk suggests that we may expect it to be elicitable from a person with the quadriceps in a normal state of tonic innervation apart from any effort at voluntary activation of the limb. Mental attention and preoccupation must be stabilized as far as possible since quantitative measurement of these conditions is impracticable. The person from whom records were being taken was introduced to the conditions of the experiment, including the eliciting of general responses before any one of these was photographed. While each record was taken he was asked to watch the shadow thrown across the aperture of the camera and to notice its movement. This was suggested to the subject as being of interest to himself rather than of importance to the recorder.

The effects of general fatigue were avoided by recording from patients who had not been recently and strenuously active; the above evidence on this subject justified the assumption that the reflex itself suffers on repetition no degree of fatigue which would vitiate the comparison of successive records in a series of moderate length such as was here obtained.

That the reflex may be inhibited seems clear, and the disposition of the limb must be such that this inhibitory effect is minimal; comfort, voluntary relaxation and an unstretched position of the hamstrings are the chief conditions thereby dictated. The above summary of the modifying factors suggests that if these conditions are complied with no other peripheral changes occurring simultaneously with the effective stimulus need be taken into account as being likely to affect the response.

The Time Relations.

Each part of the nervous pathway requires a certain minimal interval of time for its activation, and for the passage of the excitation through it to the succeeding component of the reflex arc. It is clear that the total latent period of the knee-jerk cannot be less than the sum of these two delay intervals.

The difference between the latencies of various tendon responses and between those of knee-jerks under different conditions should be explicable in terms of known variations in the component parts involved.

The Latent Period.

The extreme quickness with which the muscular contraction appears to follow the stimulus has always excited comment and measurements of the latent period confirmed this. With increasing accuracy of recording, the instants at which the blow was delivered and the first sign of response shown in the muscle, it became harder and harder to reconcile the brevity of the interval which separated them with conduction through the reflex arc.

The beginning of the stimulus has always been the easier of the two events to record, that of the muscle response has required more ingenuity and has been subject to wider degrees of approximation. All mechanical records have been delayed by inertia not only of the apparatus but of the limb segment moved as contraction continued. Mechanical records of thickening have been less subject to error from either of these sources but still to some degree distorted by both. The most accurate methods have been those employing the breaking of an electrical circuit due to thickening of the thigh (Rosenheim [72]) or movement of the foot (Tuttle [86]).

With the introduction of sensitive galvanometers and the recording of action currents in muscles, a new series of values has been introduced. These are measured from the instant of the blow to the commencement

of the action current, not to the beginning of contraction. The interval is in all cases smaller. This should be noted because it is uncertain what electrical changes are being sampled when electrodes are pushed into the muscle or laid upon the skin over its surface; not only does this "current of action" follow the blow in some cases in which no muscular contraction is visible or recorded, but there is no ground for the assumption that the electrical disturbance always necessarily precedes the contraction by the same interval of time.

The chief results of measurement of the latent period of the knee-jerk are summarized in the following table :—

LATENT PERIOD DETERMINATIONS.

Author	Method	Subject	L.P. in sigma
Gotch ..	Lengthening ..	Rabbit	5—3
Scheven ..	,, ..	,, ...	20
Waller ..	.. ..	.. ..	8
,, ..	,, ..	Human normal and pathological subjects	20—120
,, ..	Thickening ..	,, ,, ,,	30— 40
Purves Stewart	,, ..	,, ...	69—126
Tchirjew ..	— ..	Human pathological subjects	32— 34
.. ..	.. ..	,, normal subject	58— 61
Brissaud ..	.. ..	.. .. ,, ...	48— 52
,, ..	— ..	,, pathological subject	38— 42
ter Meulen ..	— ..	,, normal subject	35— 90
Sternberg ..	— ..	,, normal and pathological subject ..	less than 30
Rosenberg ..	— ..	,, ,, ,, ...	25— 60
,, ..	— ..	Rabbit	25— 25
Gotch ..	— ..	Human normal and pathological subjects	25
James ..	— ..	,, ,, ,, ...	25
Eulenberg ..	— ..	,, ,, ,, ...	24
,, ..	— ..	,, pathological subject	less than 24
Jendrassik ..	.. ..	,, normal ,, ...	23
de Watteville ..	.. ..	.. ..	20
Gowers ..	— ..	,, .. and pathological subjects	15— 90
P. Hoffmann ..	Electrical ..	.. ,, subject	21— 7
Jolly	,, ..	.. .. ,, ...	21— 3
F. A. Hoffmann	,, ..	.. .. adult	19·6—23·8
,,	,, ..	,, ,, children	14·0—17·0
Snyder ..	,, ..	.. .. subject	11·3

It appears clear that one is dealing with a response of which the latency is an important characteristic, that it is about 10—20 σ in normal cases, and that some means of recording must be adopted which will allow of time-interval measurements of this order. It has been stated that with increased facility of the response the latent period shortens, and that with other variations in stimulus or excitability it may lengthen, but the main problem is to determine what is the shortest interval which we shall be called upon to record and measure, i.e., what

is the shortest latent period for which we have good evidence? It must be long enough to allow a disturbance to have passed through the nervous system and to have reached the muscle again.

The shortest recorded latent periods under well-controlled conditions were found by Snyder [82], who, photographing the shadow of the hammer as it fell on to the patellar tendon, and measuring from this moment to the beginning of the action current shown in leads adjusted as in Piper's experiments, obtained a value of $11{\cdot}3\,\sigma$ as his minimum. The accompanying table shows that this figure lies well below that of all other workers.

It is known that contraction frequently follows direct percussion over the main mass of a muscle, and it is important to determine if such an effect can in any way complicate or distort the true reflex response which we intend recording.

A comparison of these two types of response (see Appendix II) shows that their dissimilarity both in time and in form would make the recognition of distortion from this source quite simple should it occur, and that the direct local contraction can only be elicited from percussion over the body of the muscle and not from the aponeurosis or tendon.

Method and Apparatus employed.

The conception of the knee-jerk as a fractional part of the general myotatic response to stretch shown by the vasto-crureus muscle will be seen (Appendix I) to depend upon a variety of data, partly clinical and partly experimental. It has already been pointed out that the clinical observations are open to more than one interpretation, and give in themselves no conclusive evidence in support of the reflex nature of the tendon responses. The experimental results which really substantiate this view are derived from a comparative study of the forms of mechanical contraction exhibited by the muscle in response to different stimuli, in particular those which follow varying degrees of passively produced stretch and direct electrical stimulation of the motor nerve.

The applicability of such results of experimental physiology to an understanding of variations in the human knee-jerk must remain a matter of surmise, however probable their validity may be, until comparable records have been obtained in adequately controlled circumstances from the reflexly contracting muscle in man.

The apparatus employed in obtaining the following results was devised in the attempt to obtain from intact human muscle in living subjects contraction records comparable with those already obtained

from experimental animals whose muscles may be freed from their insertions and attached to some recording lever.

A full description of this apparatus and of its use may be found elsewhere [67A]. The advantages there claimed for this method are:—

(1) The smallness of the inertia and momentum of the moving system.

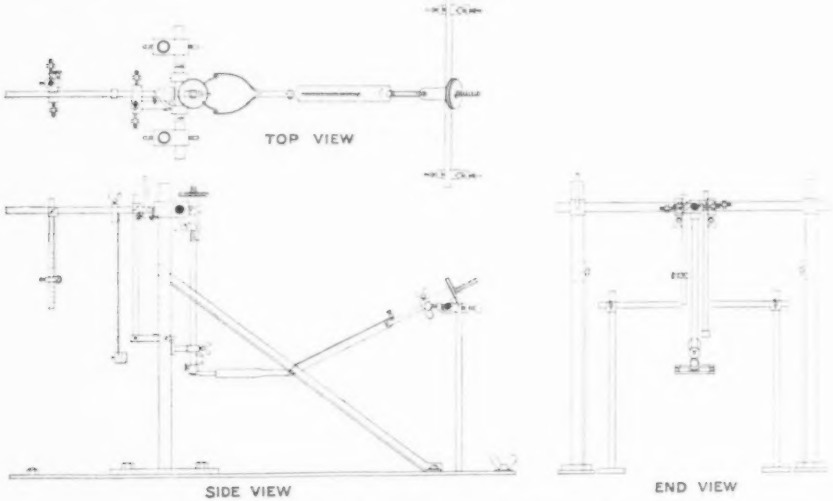


FIG. 1.—A line drawing of the apparatus used.

The subject sits upon a substantially built table clamped to a bar bolted through the wall. He reclines against an adjustable back rest and extends both legs along the table. The leg from which records are to be obtained is strapped firmly to a padded back-splint which is in turn bolted to the table in such a manner as to allow of its being raised and lowered but not moved in the axis of the limb. Two rigid, strutted vertical pillars, one on either side of the table, carry a horizontal member upon which is hinged a vertical bar free to swing in the direction of the table's length. This bar is extensible and its length controlled by a screw collar at the upper end. At its lower end it carries a piece of iron shaped like an undercut horseshoe, the lower end of which can be made to engage behind the upper border of the patella. At the foot of the table another horizontal bar supported upon vertical pillars carries a rod ending in a spring balance. The free end of the spring of the balance is connected to the horseshoe by means of a light aluminium frame. By means of a screw collar at the fixed end of the spring balance this can be drawn towards the foot of the table. Extending the spring and pulling down the patella provides any desired degree of tension in the quadriceps femoris muscle in whose tendon it lies. If the muscle is stimulated to contract under the above conditions the patella is pulled towards the head of the table against the tension of the spring, and the vertical bar carrying the horseshoe-shaped clamp rotates about the horizontal axis of its hinge. It is the movement of this bar which is recorded optically upon a falling photographic plate. To provide the necessary increment of tension or of length in the muscle for eliciting a knee-jerk, a rubber-faced hammer carried by a laminar spring was arranged to strike upon a circular metal plate fixed to the bar, whose movements are recorded. The upper end of this spring is movable along a horizontal support which carries also a catch for holding the spring in any required degree of deformation and releasing it at the right moment and a ratchet which is knocked over as the spring passes on its way to deliver the blow and which, catching it upon the rebound, prevents its giving more than a single blow transmitted to the patella. The impact of the hammer drives the horseshoe support towards the foot of the table, and thus gives a sudden stretch to the muscle.

(2) The functional isolation of the muscle which records independently of any other muscles.

(3) The ease with which the tension in the muscle may be adjusted and determined as a pull upon its natural attachment and in the functionally normal direction.

(4) Distances upon the record are directly proportional to changes in length of the muscle at all stages of contraction.

(5) It provides a comparatively close approximation to those experimental conditions under which similar work has previously been done on animals.

The photographic records obtained show the following characteristics:—

(1) A period of resting equilibrium with the muscle under some initial tension.

(2) A descent of the curve corresponding to sudden lengthening due to the blow provided.

(3) An ascent corresponding to contraction of the muscle.

(4) A plateau of maintained contraction.

(5) A descent of the curve following relaxation.

(6) In some cases, a series of after-contractions.

The Results obtained.

Occurrence.—The material available consisted entirely of hospital patients, and was not suitable for any estimation of the percentage failure to elicit knee-jerks in otherwise normal subjects. Nothing remains to be added to the figures already arrived at by others from hundreds—in one case thousands—of persons.

It was found that the knee-jerk obtained in the usual way by percussion over the patellar tendon with the knee in a semiflexed position was present in many cases in which the "suprapatellar jerk" could not be elicited. The reverse was never found to be true. In general, the reflex excitability had to be higher before percussion over the upper border of the patella became adequate—it never failed to evoke a contraction when the tendon-jerk itself was more facile. These differences are probably due to the altered position of the limb in the two cases, i.e., semiflexion when the tendon is hit and full extension when the patella itself is struck. In the latter position the hamstrings are fully stretched and reflex inhibition from this source maximal; in the former they are relaxed and the inhibition very much less.

Two observations support this view. It is well recognized that the

Achilles jerk is always difficult and often impossible to obtain with the leg fully extended. In practice the knee is flexed before any attempt is made to evoke the reflex, and a clonus which has been established, and is continuing regularly in this position, almost invariably ceases immediately the knee is allowed to extend. Again, it was here found that in some cases in which percussion over the upper border of the patella failed to produce any response while the patient was sitting up, this became effective directly he was placed supine. This presumably achieved a similar relaxation of the hamstrings "from the other end," as it were, by extension of the hip. Unfortunately the discomfort of this position over an extended period did not allow of its being used as a routine when the patients were registering in the apparatus.

Facilitation.—No extended observations have been made upon this subject—the uncontrollable factors of attention, apprehension, general comfort, etc., were stabilized as much as possible at the beginning of each set of readings, and since they do not admit of quantitative variation and measurement no attempt was made to study their individual effects. In a few cases in which a series of responses had been elicited with ease and regularity, the subject was asked to make a forced grasping movement and the stimulus repeated. The curves show that when the response was not already maximal an increase in height followed this manœuvre, and when the excitability was low or the stimulus inadequate the addition of this voluntary movement to the other conditions raised the excitability sufficiently to make the stimulus adequate.

Inhibition.—The effect of reflex inhibition from extension of the hamstrings has already been mentioned. The only other form of inhibitory stimulus used was faradism of the ipsilateral popliteal nerve. This did give a very definite decrease in the excitability sufficient in some cases to extinguish a response otherwise present, and in others to produce a diminution in the height of the contraction observed.

Variations in stimulus and initial tension.—No response can be elicited from the non-extended muscle—some degree of background stretch is always necessary, and for normal subjects an initial tension of about 300 grm. wt. was required before any stimulus became effective. With increased facility of the response a lower initial tension sufficed—with average stimuli this decreased to about 100 grm. wt., or rather less—in some cases a sufficiently heavy blow evoked a contraction before the spring extension registered any pull at all. These were invariably cases associated with a considerable amount of spasticity and the presumption

is that the active tonic activity of the muscle provided a background of reflex excitability sufficient for a heavy stimulus; in cases of less or of no pathological spasticity the actively developed tension had to be supplemented by greater degrees of passive pull before the excitability was raised sufficiently for any stimulus at all to be adequate.

It was rarely found possible to extinguish the response altogether in normal subjects by means of a very strong pull on the patella, but although high passive tension was in this way ineffective, cases were found in which the spasticity was so great that the muscle appeared to be already maximally contracted, no further contraction being observed when the patella was struck. In such cases a response in other muscles—e.g., the adductor of the same and of the other side—usually followed, and showed that the stimulus had set up a disturbance whose reflex effect was only occluded in those muscles already in maximal active contraction. These cases, further, were often those in which clonus was to be recorded as occurring either spontaneously or in response to the slightest added passive tension even when slowly applied.

When the initial tension was gradually increased in steps between 200 and 500—600 grm wt., and the force of the minimal adequate stimulus was measured, it was found that for such lower ranges of tension these two quantities were roughly in inverse proportion, i.e., as the initial tension was raised a smaller stimulus became effective. This may be explained in two ways. It may perhaps be that some minimal tension must be established in the muscle in order that the end organs should be stimulated and that this minimal tension is reached by the summation of the initial tension with the increment provided by the blow, so that when the initial tension is low the increment of tension must be greater and *vice versa*. On the other hand, it may be that the degree of reflex excitability which acts as a background for the response is increased progressively with rise of the initial tension, so that a smaller stimulus gradually becomes more effective. The evidence obtained from measurement of the curves favours the latter view, because when the initial tension is below the minimal value required for eliciting a response a very strong blow may be delivered and remain ineffectual. Yet the increment of tension which it provides, when added to that already present, gives a summed tension at the height of stimulation much greater than is actually effective on those occasions on which a very small blow gives a response when applied upon a background of slightly higher initial tension. Therefore the sum of initial and incremental tensions is not the value which determines if a response

shall occur. Further it may be seen from the accompanying curves that the size of the contraction which results is determined in each case rather by the degree of tension background than by the force of the blow. With low initial tension the contraction is of less height and of longer duration than is the case with a higher initial tension, irrespective of the size of the blow, provided this be adequate.

The decrease in the size of the minimal effective stimulus as the initial tension increases cannot be attributed to the taking up of "slack" in the muscle or in its aponeurosis. This phase of slackness, if present at all in patients from whom a tendon-jerk can be elicited, lies far below the minimal degree of stretch at which a stimulus, however great, is adequate. Also over the range of increasing initial tension for which the above inverse relationship holds good, the passive tension and the degree of stretch which it provides vary in a way which clearly denies the presence of any such slack.

Thus we may infer that over a lower range of increasing initial tension the gradually increasing background of stretch reflex in operation produces a state of increasing central excitability which both makes a smaller stimulus effective and leads to a change in the character of contraction elicited. This change is from one of lower, longer duration to one of higher, shorter duration.

This is in accord with the results in cats obtained by Fulton and Liddell, and can be explained, according to Denny Brown [15], by the observation that with low central excitability the units of low threshold respond and that as this excitability increases proportionately more and more units of higher threshold become activated. The low threshold units, innervating as they do the slow red muscle fibres seen chiefly in the crureus part of the muscle, give the contraction of less height and longer duration which has been observed. The high threshold units innervate the pale, rapid muscle fibres which increase in proportion to the others as we pass through the different parts of the muscle from the crureus where they are minimal, through the vastus internus, the vastus lateralis to the rectus femoris, where their proportion is greatest; these pale, rapid fibres supply those higher contractions of shorter duration which are characteristic of the curves obtained at higher initial tensions. This is corroborated by the well-known fact that with low excitability and knee-jerks which are obtained only with difficulty, the first indications of a response are palpable, and later visible, contractions of the vastus internus of strength insufficient to raise the leg or change the position of the patella—just a momentary thickening of this part of the

muscle. It is possible that the crureus (vastus intermedius) contracts minimally still earlier, but being nowhere subcutaneous its individual effect cannot be isolated by inspection or palpation. As the excitability of the reflex increases and the force of the contraction becomes greater the participation of other parts of the muscle-complex becomes obvious.

When curves are obtained from recording such contractions with increasing excitability the character of the jerk has been seen to change from the long, low type of curve to the quick, high type. This does not indicate that the units of low threshold and their slow, red muscle fibres which are activated with low reflex excitability fall out of operation as this increases, the higher units alone being reponsible for the contractions then obtained. They still contribute to the response, but since the form of the curve is dominated by the quicker elements the plateau remains flat and the angle sharp, and their contribution is probably only visible in the later stages of relaxation. That the response may remain isolated to the red slow units has been shown by Denny Brown for the cat, in which the composite parts of the muscle may be separately registered. There he found that when the units of high threshold alone are stimulated, the tendon-jerk as well as the response to slow stretch may spread from them to give response in the low threshold and slow red muscle fibre mechanism as well, but that the reverse spread does not happen.

It has been said that the above inverse relation between adequate stimulus and initial tension obtains over a certain range of lower tensions. At the upper limit of this range further increase in tension fails to lower the value of the minimal adequate stimulus and, in fact, with increasing degrees of initial tension the stimulus, to be effective, has to be further increased, until a tension is reached beyond which the jerk is completely occluded, however great the stimulus within the limits of tolerable painfulness.

This reversal of the relation between initial tension and stimulus may indicate that the contribution which passive tension can make to the central excitability is limited and that when its effect is maximal, and therefore also the potency of a given small stimulus greatest, any further increase in passive tension serves merely to make any constant additional increment relatively smaller and therefore increases the absolute size of that increment of tension (i.e., the stimulus) necessary to produce an effective lengthening The stretch units engaged in postural, reflex, tonic contraction will also be increased progressively in number and, since the size of the knee-jerk may be taken as a measure

of the number of units still available for this postural contraction if further stretch is applied (Denny Brown), if still more of the total number present in the vasto-crureus are already in action, i.e., if the central tension is still further increased, the numbers remaining available will become progressively diminished and the tendon response will again diminish in size. The stimulus will then have to be much increased in order to excite a sufficient number of the few remaining inactivated tendon organs.

One other allied observation made by Denny Brown has not been made in the present work. He found that in progressively stretching a composite muscle such as the vasto-crureus a tension was reached at which the tendon-jerk was completely occluded. When the tension was still further increased from this point the tendon-jerk occasionally reappeared; then the tension has to be very much further raised in order to make it disappear again. This he considered due to an unequal distribution of tension, and consequently of stretch background, in the different heads of the muscle; the tendon-jerk in the lower threshold heads becoming occluded before the excitability of those of higher threshold is reached. That such a sequence of events could never be detected in human subjects may be due to the pain which was caused by higher degrees of passive extension—this preventing a sufficient increase of the stretch necessary to render available the units of higher threshold. Much more probable is the assumption that there is in man no tension interval separating the units of low and high threshold, associated with the more complete mixing of pale and red muscle elements as well as more extensive differentiation of the muscle fibres themselves into pale elements.

The Latent Period.

This has been found to vary considerably from one normal individual to another and within narrower limits with one subject at different times. The variations shown by the same person on different occasions, i.e., on different days, were less than the mean variation between different persons, i.e., each tended to have a characteristic average latent period about which the values obtained on different occasions varied slightly.

From the series of normals examined no conclusions could be drawn as to the particular type of individual who tended to show a short rather than a long latent period. No evidence could be found for any shortening of this interval with increase of the stimulus or of the initial tension in the muscles. For any given person it appeared independent

of both factors. Where facilitation was used to increase the size of a response no shortening of the latent period was observed. Again, in none of the records taken from patients with a variety of diseases of the central nervous system could any change in this delay-interval be made out to be characteristic of any particular lesion. Neither spastic cases nor hypotonic cases showed any typical changes common to the records obtained from either group.

The curve of ascent.—It has been pointed out earlier in this paper that the rising phase in the normal contraction record is mainly rectilinear. Generalizing this statement so as to include all the records obtained, it is found that this curve of ascent is sigmoid in shape, commencing at the point of departure from the underlying oscillation curve, with a diminishing concavity upwards which disappears completely as the curve becomes strictly linear. The curve remains linear for a varying distance until it is joined to the plateau by a part which is convex upwards. In the contraction curves obtained isometrically by Balliff, Fulton and Liddell [3] from isolated muscles, there is no strictly linear phase in the ascent, this being composed of only two parts, a preliminary concavity upwards which merges at the "point of inflexion" into the main part, which is then throughout convex upwards—this convexity gradually increasing until the plateau height is reached. It has been shown by these authors that the preliminary concavity upwards corresponds to that part of the contraction process in which the recruited muscle units are overcoming internal friction and viscosity, and therefore that the duration of this phase will depend upon the rate and extent of recruitment, so that the lowness of the point of inflexion is a measure of the simultaneity with which the muscle fibres are stimulated.

It was found from the curves here obtained that when the same stimulus is applied with increasing amounts of initial tension the point which corresponds with this angle of inflexion, i.e., the point where the ascent first becomes rectilinear, occurs progressively earlier and that this change is still more marked when the initial tension is kept constant, and the size of the stimulus is increased. This would appear to suggest that simultaneity of stimulation of the muscle fibres is favoured by an increase both of the stretch background and of the size of the stimulus. Regarding the knee-jerk as the result of a sudden synchronism of the afferent units already activated by the preliminary passive stretch of the muscle, it is to be expected that both the above effects will be shown; because with increase of the background stretch

there will be many more stretch units in action and the number of afferent impulses per second will be increased, so that more of these will be thrown with synchronism by the same sudden additional stretch. Increase of the stimulus means that the hammer is travelling faster when the blow is delivered, so that more units will be effectively stimulated in a shorter time. The effect of the background stretch is seen not only as the initial passive tension is varied in a normal individual, but also as the active component of the tension fluctuated in different subjects. Comparing the curves obtained with the same passive initial tension and the same stimulus from different persons, we find that in cases of well-developed spasticity the angle of inflexion is lower than in the normal, while in hypotonic cases it is higher.

The linear portion of the ascent curve which is normally present is seen also in spastic cases, but tends to be characteristically absent in hypotonic cases, in which it suffers diminution by being encroached upon both by the preliminary concavity and by the final convexity, upwards. In these hypotonic cases the convexity begins earlier and is much less sharp, being associated, as we shall later see, with absence of any true plateau.

From those records which show a well-marked linear rise it is possible accurately to measure the slope, i.e., the amount of shortening and of tension development per unit interval of time. In the table where this is recorded the slope is given in millimetres of shortening per sigma. Variations in this slope have been compared with those of the corresponding slopes of relaxation of the same records and with changes in the height of the curve. It has been found that as the stimulus is increased with constant initial tension and the total height becomes greater, the ascent slope becomes more nearly perpendicular, and that in general the same change occurs with increase in central excitability, i.e., the slope of the rise in spastic cases is greater than in normal cases: with diminution in the excitability it is less. It is less also in cases of Parkinsonian (extrapyramidal) rigidity.

In all these cases there is no correlation between the slopes of contraction and relaxation. If increase of the passive initial tension provided merely an increased tendency towards passive extension of the muscle, then the load against which the muscle contracted would be greater, and the restoring force providing relaxation when contraction had ceased would be increased. An inverse relation between the slopes of contraction and relaxation would, therefore, be expected. Such, however, is not the case and, in fact, as the initial tension increases

over a certain lower range with constant stimulus the slopes both of relaxation and of contraction become greater, i.e., those parts of the curve become more nearly perpendicular to the base line. This also bears out the supposition that increase of the background of stretch activity provides a greater degree of simultaneity of activation and hence more rapid contraction. The total height of the curve is more properly a function of the ascent phase than of the plateau, it is a measure of the degree of contraction. It increases with increase of the stimulus, as would be expected. With constant stimulus and rising initial tension it at first increases and later decreases. The range of initial tensions over which this increase of height continues is the same as that over which an addition to the stimulus will heighten the response, i.e., it is the range over which increased simultaneity results from an increase of the background of stretch activity. Beyond this range the height of contraction decreases with rising initial tension, both because of the effect of loading in diminishing the extent of contraction in a given time, and because more and more motor units become occupied in full "postural" activity against the background tension, and fewer remain available for increasing the contraction still further when the jerk is elicited. Over this range, the size of the knee-jerk is, in fact, a true measure of the number of motor units still available for either the tendon reflex or further postural contraction (Denny Brown).

The plateau.—The curves of contraction and of relaxation are normally joined by a horizontal plateau of varying extent. The characteristics of such a plateau are its flatness, its duration and the sharpness of the angle by which it is ended.

The flatness must correspond to a period of maintained shortening in those fibres which have already contracted—it is clear that the apparatus can contribute nothing to this feature and that in fact all the forces at work outside the muscle tend towards its disturbance. The records taken from any one person show that this characteristic tends to be better marked when the initial tension is higher—this also is an effect which follows from the increased simultaneity of contraction in the muscle fibres provided by a higher background of reflex stretch activity. The same increase of flatness of the plateau is seen when the tension is constant and the size of the contraction raised by increasing the stimulus, and the mechanism of these effects is probably identical.

It is a variation in the plateau which has been found to be one of the most constant characteristics of certain types of disease of the central nervous system. In spastic cases it is invariably well marked and can

be relied upon to appear with certainty even in smaller responses. In hypotonic cases there is seen a rounding of this part of the record which may be so complete that no true plateau can be said to exist at all. A similar rounding is seen in cases of severe Parkinsonian rigidity, but never to the same extent as in hypotonic cases.

The duration of the plateau does not alter characteristically with responses of the same height from different persons with comparable degrees of reflex excitability, but two constant forms of variation can be seen. In the same individual the duration of the plateau decreases as the height of the contraction is increased and becomes shortest when this is maximal. In two different normal persons, if the stimulus required to elicit a response of a given height is greater in one than in the other, then the plateau will be shorter in the curve obtained with the greater stimulus. This probably means that in the person whose reflex is more easily elicited by a smaller stimulus more units of lower threshold are activated and the curve is produced mainly by slow red muscle fibres which provide a longer plateau. This is borne out by the observation that the two curves of the same height as above obtained have other differences which can be traced to the same origin, e.g., the angle of inflexion is higher and the slope of ascent less steep in the curve with the longer plateau.

In animals Fulton [25] described a flat plateau terminating in a sharp angle for both the muscle twitch and isometrically recorded knee-jerk, and further said that "It seems probable that a muscle allowed to shorten isotonically also exhibits a flat top and a characteristic angle." He showed from his records that the duration of the plateau of the isometric knee-jerk increases with increase of the initial tension, and confirmed Lucas's [50] findings that the plateau is of longer duration in the case of the knee-jerk than of the muscle twitch and longer in the case of submaximal than maximal response (Fulton [26]).

In the majority of records from normal persons the angle which ends the plateau is well marked and abrupt. It is present whether the response be maximal or submaximal, of the high short plateau or the low long plateau variety, but is usually better marked in the former. In all the records taken it is seen best in the muscle twitch elicited by stimulation with a break shock over the motor-point, and it is lost in all those cases in which the plateau is not in evidence. Fulton holds that since "contractile energy ceases at the angle," its sharpness may be taken as a measure of the simultaneity of relaxation of the muscle fibres. Its association in this series of records with a low point of inflexion on

the curve of ascent and a fairly abrupt junction between the linear ascent curve and the plateau bears out this view, as does also the still greater acuteness of the angle obtained from the motor twitch.

The curve of relaxation.—Following the angle, the descent from the plateau is normally linear for the greater part of relaxation, merging fairly abruptly into the base line. The strictly linear part of the curve is better seen in relaxation from curves of greater amplitude, i.e., from plateaux of greater height, but it is almost invariably true to describe this part of the record as being normally always concave away from the base line except where the slope is constant. If we agree with the above recorded observations of Fulton, that "contractile energy ceases at the angle," we may assume that the course of relaxation is determined by the passive force tending towards extension as provided by the spring of the balance used, and opposed by the internal friction and viscosity of the muscle. This we should expect to provide a slightly accelerated curve if the extending force were constant, but since the record is not strictly isotonic this force falls off slightly but progressively with increasing extension and the accelerated character of the fall is lost. It is clear that in the final degree of extension at which further relaxation is arrested the extending force is opposed not only by the above internal resistance but by the tonic postural contraction of the muscle. It is this force which provides the terminal concave part of the curve of relaxation and brings the system to rest at the original base line.

In most of the records the resting length of the muscle was the same before and after the jerk, and any departures from this retention of resting length were in the upward direction, i.e., the curve did not fall quite to the original level but remained slightly above it. This was first interpreted as being due to an imperfection of the apparatus which allowed some alteration of the relative positions of the patella and of the frame which was attached to it. Since this, however, would be more likely to lead to a slipping of the frame towards the foot in which direction it was pulled by the spring, it is more probable that some explanation along the line suggested by Veits can better account for this slight increase of the maintained contraction when it occurs. This author found that there is an optimum set of tonically innervated muscle, and that following the subsidence of a clonic contraction there may be a readjustment of the length in the direction of this "optimum set," unless this was previously present, leading to a maintained slight shortening or slight excess lengthening.

The total duration of lengthening did not vary consistently in any

way with the size of the response in normal persons, but it showed a definite decrease characteristic of hypotonic cases, and an increase in those of extrapyramidal (Parkinsonian) rigidity. Variations from the normal linear curve of relaxation were of two types. The first occurred in those cases of hypotonus in which, associated with an abnormal curve of contraction and the absence of any true plateau, there was found a sigmoid curve of relaxation in which a strictly linear phase was absent or minimal. The other type of variation produced a record of which the descent was convex upwards for its greater part and the concave terminal phase followed directly upon this initial convexity. This holding-up of relaxation obscured the "angle" at the end of the plateau, but that it was not due to increased asynchronism of the motor units innervated was shown by its occurrence invariably in curves of which the ascent and plateau were in every way normal. It was seen in records from normal persons only under exceptional conditions, but was characteristic of those from cases of spasticity associated with pyramidal tract lesions. Its nature is clearly revealed by the circumstances in which it was produced.

In cases of slight spasticity with increased facility of the tension reflexes a response could be elicited and recorded at low initial tension of the muscle which was in every way normal, the curve of relaxation being strictly linear. If responses were recorded with progressively increasing tension it was found that the convexity or delay of relaxation appeared and became gradually more pronounced. With an increase of this feature there appeared definite, small after-contractions, either delaying the later parts of the relaxation curve or being added on to the curve after relaxation was complete. With further increase of the initial tension these increased in size and total number until in favourable cases a single stimulus sufficed to elicit not only the initial contraction with a plateau of normal height and flatness, but also a series of indefinitely persisting after-contractions which occurred at a regular rate. Clonus had been established. Measurement of such records showed that the convexity upon the curve of relaxation preceded the first clonic contraction by the same interval as separated each beat of the clonic series. It appears reasonable to assume, therefore, that its appearance is due to the same factor which, when more pronounced, leads to persistent clonus. It is thus probable that it is not a persistent tonic after-effect tending to maintain shortening at plateau height, but is a clonic or phasic element occurring in these records immediately after the plateau and the same as the "hump" of Balliff, Fulton and

Liddell [28], or the "nose" of Fulton [27]. Its presence is associated with increased facility and hence with increased height of the response, is characteristic of spastic individuals and always precedes the appearance of a persistent clonus.

Clonus.—In some persons an optimum initial tension can be found at which a single blow will elicit a knee-jerk followed by a rhythmic series of contractions which persist as long as the tension is maintained. The average rate of this clonus was found to be about 8·5 sec. The rhythm was perfectly regular for any one person so long as other circumstances were not altered, and although at its inception there was a gradual increase in amplitude during the first few contractions, the rate did not similarly increase; nor did it later decrease in those cases in which the clonus desisted spontaneously. In the cases observed such clonus was only found where the tone of the quadriceps was quite definitely raised to passive manipulation, and clinical spasticity was well marked. When this spasticity was extreme it was often found possible to bring it out by a steady stretch of the muscle and in a few persons clonus alternated with periods of spastic contraction while the limb was lying free upon the experimental table. As a general rule the higher the degree of spasticity present and the greater the facility with which clonus was elicited, the more rapid was its rate, but a rhythm of more than 12 sec. was not seen. Since the limits of initial tension between which persistent clonus could be evoked were narrow it was not possible to state definitely that the rate was uninfluenced by the tension present, but this was certainly the impression received from observations made. It was invariably found that a slightly painful stimulus to the sole or skin of the same leg abolished it when once established. Attempts were made to facilitate its appearance by passive dorsal-flexion of the ankle, since it had been found that in some cases the tone of the quadriceps may be thereby definitely increased as in the Stutzreaktion of reflex standing [67], but no change was observed as a result of this manœuvre. The fact that it appears in those cases of which records at a lower initial tension are characterized by a "hump" upon the curve of descent suggests that it arises from an exaggeration of the same process to which the hump itself is due, and the time relations show that the hump may be regarded as the first of an abortive series of clonic contractions.

The relation of clonus to the knee-jerk has always attracted attention, and a tendency to regard the underlying mechanism as identical has gradually emerged. Before the tendon reflexes were themselves

described, ankle-clonus occurring spontaneously had been studied by Brown Séquard and, as evoked by a sudden stretch, had been applied clinically under the description of "épilepsie spinale" by Charcot and his co-workers. In his original paper Erb showed that knee-clonus could be elicited in favourable cases by depressing the patella from above, but he regarded this as being a distinct type of response not to be confused with "a knee-jerk of clonic form." Sternberg in commenting upon the phenomena considered it to be a rhythmic response of stretched muscle of which the relation to the knee-jerk was not clear. He attributed it to the working of some preformed, central mechanism for rhythmic reflexes, and describes it as being probably a spinal form of the tension reflex.

Many observers have since studied the conditions under which it arises and the rate at which it occurs. Veits, working with cats, considered it to be characteristic of decerebrate and not of spine preparations; although it could be elicited in spinal cats by means of the facilitating influence provided by stimulation of the crossed peroneal nerve. These observations referred to the clonus which followed a simple knee-jerk elicited in the ordinary way by a blow, i.e., a persistent clonic after-discharge, which he did not regard as of the same origin as the spontaneous clonus which he found to occur in spinal as well as in decerebrate preparations. The knee-clonus following a tendon-jerk in cats he found to be established at a rhythm of about 11·5 sec. In man the rate was lower—about 8·8 to 9·7 sec. In discussing its mechanism and the supposed tendency of the motor centres to rhythmical discharge, he pointed out that it has nothing to do with stepping movements, for these proceeded at a much slower rate, and that if clonus were simultaneously established in both quadriceps the contractions on the two sides were synchronous and not alternate. He found that for any one preparation the limits of the "tone" (? active muscle tension) between which it could be elicited were narrow, and included that assumed "optimum set" of the muscle to which reference has previously been made.

From his simultaneous electrical and mechanical records of ankle-clonus, Wertheim Salomonson [94] concluded that it was a series of simple muscle twitches, each preceded by a single current of action which tended to occur under conditions of increased muscle irritability and a certain degree of tonic contraction. He timed the first few of the series of contractions, and found the second beat to occur only 0·25 to 0·3 sec. after the blow was delivered. On measuring the

duration of the first contraction he found this to be 0·2 to 0·3 sec., but did not go on from this to deduce any other relation between the initial and subsequent contractions. Sherrington held that "the stretch eliciting clonus can be regarded as one temporarily relieved by each contraction of the muscle itself and becoming operative again as each contraction subsides," i.e., each beat of the clonus is set up by renewed stretch during relaxation from the previous beat. A more accurate analysis of the electrical and mechanical records of the muscle in clonus now shows this view to be untenable.

Denny Brown [15] describes the phenomenon as a regular synchronous discharge which, while being most commonly set up by a tendon-jerk, is often seen to occur spontaneously in preparations with well-developed decerebrate rigidity, in which case also there may be seen spontaneously alternating phases of tonic and clonic activity. His records show a series of twitches in varying degrees of fusion accompanied by regular, large action currents. He finds that its appearance is favoured by allowing greater shortening during contraction, since the plateau after action is thereby reduced and relaxation increased, and also by the presence of a highly developed, stretch-reflex background. The optimum tension that provides this strength reflex must be partly active, for a certain degree of tension organ excitation is necessary to provide the proprioceptive inhibition which in his view determines the appearance of clonus. With higher degrees of tension background the individual twitches suffer greater fusion and the simultaneous action currents occur proportionately earlier and earlier until they can be shown to occupy such a place on the curve that the wave of afferent impulses to which each is due must have originated peripherally before relaxation from the previous beat commenced. Regarding, as Denny Brown does, this afferent volley as being set up by tension in the muscle fibres, it may be expected to arise at the period of greatest tension change, i.e., during contraction and relaxation. The afferent volley, therefore, which finally overcomes the barrier of proprioceptive inhibition and leads to the discharge of a further large efferent disturbance, cannot have been set up by the previous relaxation which occurs in many cases later than this action current, and must have originated in the previous contraction phase, or even partially during relaxation from the still further preceding clonic beat. The view that the action currents represent in this way a series of rebounds from proprioceptive inhibition explains the value of a tendon-jerk for their initiation, and the presence of a hump upon the curve of relaxation at lower tensions can be under-

stood as being indicative of a tendency to clonus at higher tensions, since it merely gives evidence of simultaneity of relaxation in a majority of the units activated. This author finds that there is a special predisposition to clonus in the "spinal" state, where perfectly regular rhythms may be present at quite low tensions.

This fascinating study by Denny Brown of clonus as a form of discharge set up and maintained by a myotatic mechanism and dependent upon rhythmic release from inhibition of the spinal centres, shows us that the very first description of this phenomenon as "épilepsie spinale" was not as inadequate as the plausible, but really unsound, explanation which later supplanted it.

THE CHARACTERISTICS OF DIFFERENT VARIETIES OF KNEE-JERK.

Pyramidal tract lesions.—The changes typical of records obtained from such cases may show themselves to be unmistakably present at a stage of the disease when clinical examination reveals no demonstrable spastic resistance to passive movement. There is increased facility of the reflex shown by its appearance with both lower initial tension and smaller stimulus than normal. For the same values of tension and stimulus the response is of greater amplitude, it has a more nearly perpendicular curve of ascent, invariably a well-marked flat plateau and the curve of relaxation shows a preliminary convexity or hump which may be followed by one or more secondary clonic contractions.

No characteristic differences have been found to distinguish the responses occurring with lesions at different levels of the pyramidal tracts, but it may be stated as a generalization that their common characteristics are better emphasized in spinal cases than in decerebrate cases (hemiplegia, etc.), i.e., the amplitude is on the whole greater, the hump better marked, and the tendency to clonus more definite. This is in accord with some but not all of the results obtained from a comparison of the spinal and decerebrate tendon reflex in animals. Thus Balliff, Fulton and Liddell [3] found that the latency was greater in the case of the spinal knee-jerk, the requisite initial tension or adequate stimulus was larger, the total duration of the response longer, the point of inflexion on the ascent was higher and the curve of relaxation showed no hump. Sherrington agrees that the spinal reflex has a higher threshold for stimulation. Denny Brown and Liddell have shown that some stimuli which can inhibit the spinal supraspinatus jerk are weaker than those requisite for inhibition of the jerk in decerebrate preparations, while Cooper and Adrian agree that the after-

discharge which they found characteristic of the decerebrate jerk is absent from the spinal jerk. In his most recent paper Denny Brown finds that the "spinal state" predisposes more than any other nervous condition to the presentation of clonus "at almost all tensions," and the hump which "indicates a tendency to clonus" would there be expected to be well marked, so that the evidence of comparatively recent work is not unequivocal.

Hypotonic cases.—There is in general an increased difficulty in obtaining a response from such cases which may amount to complete absence of the jerk. But this is not always so, and in some persons in whom the resistance to passive movement is minimal and the limb almost flail-like on shaking, quite good reflexes can be obtained. This may be in part associated with the hypotonicity of the flexors as well as of the extensors, so that the position of full extension of the knee which is adopted for recording does not set up so much stretch response in the hamstrings, and these therefore exert less than the normal inhibitory effect upon the appearance of a knee-jerk.

Many of the persons from whom records have been taken have shown typical "pendular" knee-jerks when these are elicited with the patient sitting upon a table and the legs hanging freely. Such "pendular" responses have always been held to be due to an absence of the normal participation of the hamstrings in determining the extent and form of the response. That the tension in the hamstrings normally increases during the knee-jerk when this is produced in the ordinary way is easily recognized even by palpation, but the relation of this increase of tension to the other concurrent events has been a matter of much dispute. Pfahl [64] held that these muscles contracted secondarily to their stretch as the knee was extended by the reflexly contracting quadriceps. Lombard [48] considered that the original stimulus—stretch of the quadriceps—provides reflexly contraction not only of that muscle but also, somewhat later, of the hamstrings. This interval between the two antagonistic contractions has been measured by Golla and Hettwer, who arrived at a value of seven sigma. Lombard further attributed the short jerky clonic reflexes which occurred especially towards the beginning of any one series of responses to the too early contraction of the flexors. Sherrington has put forward the suggestion that the hamstrings exert not only a mechanical braking effect upon the "hanging knee-jerk" (which can be diminished by denervating them and making them toneless) but also that impulses set up in the tonically innervated flexors, consequent upon their stretch during the

early stages of knee extension, react by inhibition upon the quadriceps, affecting the later part of the response. This part of the effect can be destroyed by deafferenting them, and in corroboration he cites the well-known fact that the Achilles jerk is more easily obtained when the knee is bent, i.e., when the hamstrings are relaxed.

The position of the leg and the nature of the events recorded in the present experiments, by purposely precluding all effects of the hamstrings, make it impossible to determine their behaviour during the contraction of the quadriceps, but the curves obtained show that the form of the contraction in the quadriceps alone is sufficient to account for the pendular type of response. Those curves are characteristically dome-shaped, a sigmoid curve of contraction passing over into a similar sigmoid curve of relaxation without any tendency to the formation of a plateau. The absence of any linear phase in the ascent makes it impossible to obtain comparable values for the slope of this part of the curve, but it does not appear to be markedly abnormal. The slope of the fall, however, although nowhere linear, does show an increased, general steepness of this part of the curve. The whole curve suggests a complete absence of maintained contraction and of synchronism in the individual muscle-fibres. This type of response, found here in association with unilateral cerebellar lesions, in the limbs of the same side, appears to be produced by a sudden, short-lasting, jerky contraction with an absence of maintained shortening which may be closely allied to the spasmodic contractions and lack of postural fixation shown by Holmes [37] to be clinically characteristic of such cases.

Chorea.—The knee-jerks in this disease are notoriously variable; not only are they exaggerated in some cases and lost in others not otherwise dissimilar, but in the same patient successive blows may yield totally different results without the conditions having appreciably changed. This may be in part due to the constantly varying amount of voluntary innervation and relaxation associated with the restlessness characteristic of such patients.

Apart, however, from the ease or difficulty of eliciting a response, the jerk, when it appears, frequently shows another variation. It has been described as the "sustained" knee-jerk of chorea. This may clearly be due either to an extension of the plateau in the form of persistent tonic after-effect or to the secondary addition of either clonic or voluntary contractions.

Wertheim Salomonson, recording such a jerk both electrically and mechanically, came to the conclusion that it was composed of a

preliminary simple muscle twitch to which was fused a true tetanic contraction of varying duration and a latency of 0·21—0·25 second. He suggested that chorea was one of the conditions in which some cerebral reflex centre was called abnormally into operation, the area of stimulus-reception being the skin around the patella, and the response the tetanic contraction observed.

In the records here obtained abnormal responses have been found in such cases to show two additions to the preliminary twitch, a definite prolongation of the response and the occurrence of secondary contractions. The twitch itself was frequently of the hypotonic variety with no plateau. The prolongation was not present as a plateau of much increased duration but as an abnormally delayed descent; both this prolongation and the secondary contractions do not show the same time-relations and characteristic form of the clonic elements found in spastic cases, but are larger and more spaced out. In addition, some records have shown what is undoubtedly a voluntary contraction following comparatively long after relaxation has been completed.

Extrapyramidal (Parkinsonian) rigidity.—It was, in general, found difficult to predict the degree of facility which would be shown by the reflex from a consideration of the amount of rigidity present, but as a rule it tended to show a facility which was maximal for the first few jerks elicited and thereafter to become much more refractory. It was found impossible to stabilize the amount of voluntary relaxation sufficiently for a series of constant contractions to be obtained, so that any conclusions as to their variability with different initial tensions and different strengths of stimulus would be unjustified. In this extreme, apparently spontaneous, variability of the response these cases resembled those of chorea. The curve of contraction obtained was characteristically rounded with no plateau, no trace of a terminal "angle" and a delayed descent followed by a very slow return to the previous base line of resting equilibrium.

Summary.

This paper is concerned with an attempt to examine and record the knee-jerk in man, in order to find what are the changes in this reflex typical of different diseases of the central nervous system.

A short account is given of those changes which have hitherto been recognized as appearing under such conditions. From these isolated facts of clinical observation generalization is only possible in the light of the accepted physiology of the reflex.

A summary is given of the current physiological conception of the knee-jerk as a reflex rather than as a local muscular response, and its explanation as a particular example of the general myotatic stretch reflex is adopted as the most satisfactory. The work upon which this view of the reflex is based has been done by other workers in carefully controlled experiments upon animals, and for testing its validity in the case of the human knee-jerk the conditions of recording from man must be approximated as closely as possible to those of the above experiments. It is shown that previous methods of recording the human knee-jerk failed in this respect, and it is claimed that the apparatus and method here described present a definite advance in this direction.

The calibration and errors of this apparatus are discussed and examples of the records obtained by its use are given. Inspection and measurement of these records show that the essential form of the reflex is the same for both man and animals, they reproduce the characteristics of the curves obtained from rabbits and cats, and the typical features of decerebrate and spinal responses are seen to be identical in both.

In this way the applicability of physiological data to the human knee-jerk is confirmed, and in so far as the above view of the nature of the reflex is valid the explanation of the phenomena of human muscle tone and spasticity in terms of myotatic stretch response is justified.

In addition, this method provides possibilities of detecting and recording changes in form of the reflex which are of definite clinical significance. Many of these changes are shown to characterize certain lesions of the central nervous system and their existence to be of diagnostic value. In particular those changes typical of interruption of the pyramidal tract at different levels, of extrapyramidal (Parkinsonian) rigidity, of cerebellar disease and of chorea are summarized and the occurrence and significance of clonus discussed.

This work was made possible in its earlier stages by the facilities very kindly afforded by Sir Thomas Lewis who allowed it to be carried on for a time in his department and whose technician is responsible for building most of the apparatus. I am glad to acknowledge my indebtedness also to the Physicians of the National Hospital, Queen Square, for permission to use records obtained from patients under their care in that institution; to Dr. F. M. R. Walshe, in charge of the Neurological Department at University College Hospital, for his advice and encouragement throughout; and to Dr. Denny Brown for his helpful discussion of many points.

APPENDIX I.

The Knee-jerk as a Myotatic Reflex.

From the above detailed considerations it appears that the knee-jerk is in its simplest form a contraction of the quadriceps femoris muscle evoked by a sudden stretch. This response is conditioned by the functional activity of certain nervous connections of the muscle and of that part of the spinal cord with which these are associated. It can be modified indirectly by a variety of factors—lesions of the central nervous system, drugs, etc., and can be both facilitated and inhibited centrally. There is always a short interval between the delivery of the stimulus and the beginning of the response, i.e., a latent period.

In all these ways it possesses those attributes which are characteristic of a true reflex, and it contrasts in several definite particulars with what is known to be a direct muscle response dependent upon local excitability.

Measurements of the latent period show this to be very short, and transmission of the disturbance initiated by the stimulus through the nervous system and back to the muscle can only be reconciled with these measurements if the rate of conduction along the nervous pathways has the highest value which has been suggested for it.

Since the balance of the above evidence suggests that the knee-jerk is to be regarded as a true reflex contraction set up in response to stretch of the muscle itself, it is of interest to examine how this particular reflex compares with or differs from the other known stretch reflexes shown by the same muscle group.

In 1924, Liddell and Sherrington [47] published the result of their investigations into the behaviour of muscles when stretched. They found that a muscle deprived of nervous connections reacted when slowly stretched as would a partly viscous, partly elastic solid of the same dimensions. When fully innervated, it behaved very differently. Such a muscle when slowly and progressively stretched responded by developing additional tension, which continued to increase so long as the muscle was being lengthened, preserved its increase so long as the new length was maintained, and decreased immediately the muscle was allowed to shorten again. The characteristic features of this response were the readiness with which the muscle reacted to minimal degrees of stretch, as small as 0·8 per cent. of the total length, a latent period amounting to some interval less than 20, and its dead-beat nature, i.e., the immediate fall in tension which followed either shortening or inhibition with hardly any after discharge.

Whatever the length of such an innervated muscle, these reactions—i.e., an increase of tension tending to resist lengthening and a fall of tension in response to shortening—could always be demonstrated, and they clearly favoured the preservation of the particular length or "set" of the muscle at the commencement of stretch or of shortening. These myotatic reflexes, as Sherrington called them, were considered by him to underlie the phenomenon of muscle tone, and he suggested at the same time that the knee-jerk was but a fractional example of such reflexes—the response to a stretch of extreme brevity and slightness. These very qualities determined the character of the response evoked in that the stretch being neither extended nor maintained, the resulting contraction was only transitory. If we are to accept this conception of the tendon-jerk as a fractional example of the general response to stretch, we should be able to recognize operative in its production the same mechanism as has been discovered to subserve the myotatic reflexes as a whole.

The current conception of this mechanism has been elaborated from a study of simultaneously recorded mechanical and electrical changes in the active muscle.

Such records have been made by Fulton and Liddell [28], who find that during the course of continuously increasing stretch a series of small and irregular action currents can be detected. During the plateau of maintained tension, after further stretch has been arrested, even these disappear, and the string of the recording galvanometer remains practically stationary. If the stretch either during its progressive increase or its steady maintenance be made in any way discontinuous, e.g., from irregularity of the stretching apparatus or from shaking the table upon which the preparation is supported, there occurs a sudden well-marked electrical variation corresponding to each discontinuity. The way in which such a sudden electrical variation can most readily be produced is by tapping the stretched muscle itself or its tendon. Such an action current is seen to be followed by a short "silent period" during which both the small electrical changes, if otherwise present, and the increased tension, fall away.

Since any stimulus which normally inhibits contraction of the muscle will cause its immediate relaxation from the plateau corresponding to maintained stretch, it is clear that throughout this plateau efferent discharges must be coming into the muscle to maintain the contraction, and the most probable explanation for the fact that no current of action is detectable by the galvanometer is that they are completely asyn-

chronous and never attain a measure of simultaneity sufficient to register electrically by summation of effects. It is assumed that these efferent excitations are sent down in response to a stream of impulses afferent from the muscle nerve-endings sensitive to stretch. The stretch being continuous, the afferent disturbances are uniformly spread out.

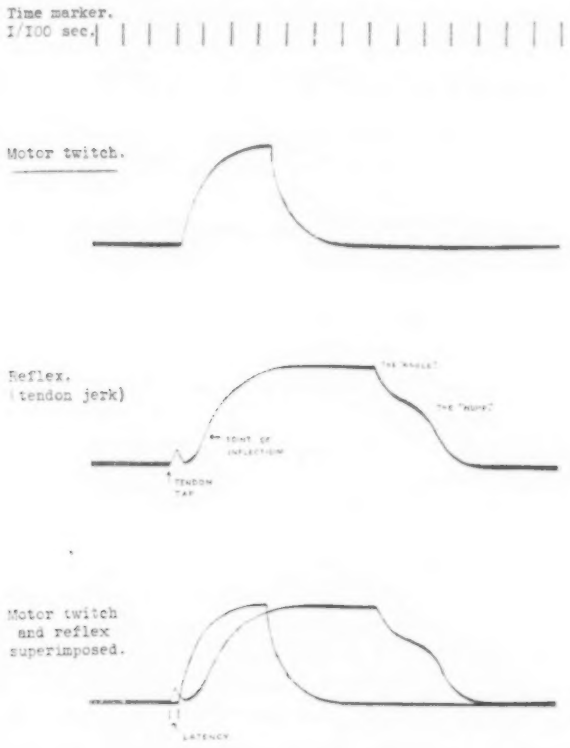


FIG. 2.—A diagram illustrating the differences between the knee-jerk and motor twitch records obtained from the cat. (After Balliff, Fulton and Liddell, with permission.)

It is clear that, if this be so, then any sudden increase of stretch will initiate in these end-organs a volley of afferent impulses, whose volume and simultaneity will be directly proportionate to the brevity and extent of this sudden stretch, so that the tap to the muscle or to its tendon, as above described, will be the most favourable way of producing a large,

nearly simultaneous volley of impulses, which return to the muscle via the central nervous system, as efferent disturbances, and there sum both temporally and electrically into one longer current of action. It was found by measurement that the resulting electrical variation occurred in the quadriceps femoris muscle of a rabbit from 6 to 8 after the discontinuity of stretch by which it was initiated.

It has already been pointed out that the adaptation of tension in the muscle to its length at any given moment is present under even slight degrees of passive extension. The sudden increase of stretch caused by tapping the tendon of a muscle under such slight passive extension—i.e., the tendon-jerk of the muscle—giving rise to a reflex contraction associated with a well-marked brief action current followed by a period of electrical quiescence, can thus be readily explained.

If we compare the mechanical and electrical changes of the tendon-jerk with those following a single maximal break shock stimulation of the motor nerve (fig. 2), we find that they both show a gradual ascent, a plateau and a curve of relaxation preceded by an "angle," and their current of action a single, large, initial electrical disturbance. But while in general form they are very similar, there are certain constant differences. Thus in the tendon-jerk the angle of inflexion on the ascent of the curve is proportionately higher up, the maximum plateau height is less, the "angle" is less sharp, the descent is interrupted by a hump and the electrical disturbances more spread out. Most of these differences can be explained as being due to the slightly asynchronous character of the efferent volley in the case of the tendon-jerk. Thus we can see that the characteristics of the tendon response are due to a degree of simultaneity of stimulation which is completely absent in the gradual, continuous, stretch reflex, and maximal in the motor twitch.

The interruption of the descent or relaxation alone demands another explanation, and it can be shown to be associated with the "silent period" in the galvanometric record: this is due to proprioceptive inhibition arising within the muscle and set up either by the occurrence of the action current itself or of some other underlying change. It lasts for a considerable period after this electrical disturbance, and its cessation coincides with the hump upon the curve of mechanical relaxation.

A more detailed consideration of the variations in the operation of the whole mechanism will be deferred until the subject of clonus is dealt with.

There is some evidence [Fulton and Liddell] for the belief that it

is the Golgi tendon-organ which is sensitive to stretch, and initiates those afferent disturbances which, summing up the origin of the motor units, give rise to the efferent impulse. Since the facility of this reflex varies considerably under different conditions, it has been assumed that these efferent stimuli sum centrally not only with one another, but with a variety of other influences, some tending towards facilitation, others towards inhibition, of the reflex. Many allied phenomena can be best explained upon the assumption that adequate excitation of the motor unit involves summation up to and above a certain threshold, and inhibition the removal of the accumulated central disturbance, whatever its nature may be. On the cessation of inhibition there will be many central junctions at approximately the same degree of summation, and also, since there is a temporary acceleration of the rate of discharge following inhibition, the chances of temporal overlap of impulses will be greater. It follows from this that the synchronous stimulation of many motor units will not only be forwarded by the synchronous arrival of efferent impulses, but will also tend to occur after inhibition. This synchronizing effect of inhibition is seen in the production both of the hump upon the descent curve of the tendon-jerk with the increased action currents which accompany it, and of clonus. The latter, occurring under suitable conditions of central excitability, may thus be regarded (Denny Brown [151]) as a series of rebounds from inhibition. This inhibition in the case of the stretch reflex we have seen above to be of proprioceptive origin, and there is good reason (Denny Brown) to suppose that the muscle spindles are the receptor organs that initiate it.

That the stretch reflex can be obtained with greater facility from some muscles than from others appears to be due to modifications not only of the conditions of summation and facilitation at the central nervous connections, but also of the purely peripheral mechanism. The distribution and threshold of the end-organs varies from muscle to muscle as does also the character of the muscle fibre itself. Thus the limb extensors, or antigravity muscles, show a much greater readiness of response than do the flexors, and within any one group, or indeed with any one muscle where this is composite in structure, we find that there is a constantly lower threshold to stretch stimulation shown by the slow, red series of muscle fibres than by the pale, quick series. The result of this differentiation is that when the total exciting agent—i.e., stretch afferent impulses summated with central excitability—is low, the red slow muscles respond alone, and as this agent increases with increase of either of its components, proportionately more and

more of the pale muscle fibres become thrown into action and the response changes correspondingly in form, with increase both of rapidity and height of contraction.

These changes are most clearly to be observed when the conditions of peripheral stimulation remain constant and the central excitability is varied. Thus it is found that the spatial orientation of the labyrinths exercises an influence upon the magnitude and facility of the stretch reflex; there is a position in which their influence is maximal and another in which it is minimal; associated with the maximal position, which presumably increases the central excitability of the reflex, we obtain a higher degree of tension development, which both falls and rises more abruptly, the reverse holding good for the minimal position. Exactly the same forms of influence result from the operation of other means of raising and lowering the central excitability—the tonic neck reflexes and cortical or mesencephalic factors.

Regarding the knee-jerk as a fractional form of stretch reflex to the vasto crureus one would expect the above conditions to be similarly operative in determining its facility and form, and such indeed appears to be the case. These modifying influences and their results have been examined in greater detail earlier in this paper and it must suffice here to mention that the generalizations above made for their behaviour in respect of the stretch reflex obtain also for the tendon-jerk. An increase of central excitability, whether from an increase of the peripheral stimulus or of the adjuvant central nervous factors, leads to a spread of the response to include units of higher threshold. The vasto crureus, with which we are dealing, being a muscle which in respect of its fibres shows a compositely graded structure with red slow elements and pale quick elements, the progressive spread of the response with increased excitation leads to easily recognizable modifications in the shape of the mechanical contraction and its associated electrical variations. With minimal central excitability the slow units of low threshold are activated by the knee-jerk, giving a curve of long duration and small tension development—when maximal the curve takes the form of a higher, shorter jerk.

These changes follow alterations in labyrinth orientation and mesencephalic influence and are conspicuous in the difference between the spinal and decerebrate knee-jerks. When the spinal centres are isolated by functional interruption of the cord proximal to them, the lowering of central excitability leads to restriction of the response to the units of comparatively lower threshold, the jerk being essentially of the low

protracted type and the reflex to slow stretch minimal in extent and facility. During the recovery from shock which follows acute interruption of the cord, the tendon-jerk can be elicited for some considerable period before slower stretches become again operative. This differentiation may be explained as being due either to increased potency of synchronism of afferent stimulation when the central excitability is low, or to the fact that with minimally developed stretch response the muscles are almost completely slack and extended so that the endomysium exerts a splinting action upon the muscle fibres and opposes to any attempt at stretch an elastic resistance which prevents stimulation of the muscle-stretch afferents unless the stretch is particularly rapid and extensive.

The converse of this picture is also true. Just as a raising of central excitability by optimum condition of the adjuvant factors—labyrinth neck and mesencephalic influences, etc.—facilitates and increases the response to slow stretch, so the presence of a background of a highly developed stretch reflex is associated with well developed, facile tendon responses. This accounts for the well recognized association between the tendon-jerks and the degree of muscle tonus and is seen with particular clearness in the case of flexor muscles. Here stimulation (e.g., to an ipsilateral afferent nerve) which when maximal causes a flexion reflex, when minimal leads to much increased facility and extent of the tendon responses in the same muscles. The observation that when passive stretch is very extensive or spasticity of the limb very great no detectable additional shortening follows a further sudden increase of tension provided by a blow on the tendon, is not inconsistent with this view. If the current of action in the muscle is taken as an indication of response it is found, even when the stretch reflex is already so much in operation—i.e., the reflex tension is so high, that the blow is followed by no further increase in tension—that there invariably ensues with the usual latency after each blow a large action current and succeeding silent period. This shows that the added sudden stretch has provided that transitory synchronism and resultant proprioceptive inhibition which is the distinguishing feature of the tendon-jerk.

These considerations lead to the conclusion that the characteristics of a tendon response, e.g., of the knee-jerk, strongly support the view that this is a true reflex contraction. It provides, of the myotatic or stretch reflexes, one example whose essential peculiarity follows from the synchronism of afferent excitation and motor innervation, and it stands in sharp contrast to those steadily maintained contractions

which are normally provided by complete asynchronism of the activating impulses.

APPENDIX II.

The Latent Period.

This time may be considered to be the sum of the following elements : the latent period of the receptors in the muscle, the time taken in conduction to and from the spinal cord, that necessary for linking up the afferent and efferent paths within the central nervous system, and finally the latent period of the muscles to direct stimulation. The time-interval between the entry of the disturbance into the cord and its emergence, called the " true " or " reduced " reflex time, since it is so much greater than would be required for the conduction of the disturbance along a nerve whose lengths were equal to the thickness of the cord, must be due to the discontinuity of the path within the cord and counted as delay at one or more " synapses " required by the intercalation of intraspinal neurones. By far the largest element of those contributing to the total latency of the knee-ierk is that due to peripheral nerve conduction, and if we are to make any valid deduction from experimentally ascertained values, as to the reduced reflex time (" synapse " time), it is clear that we must discover some reliable value for the velocity of the disturbance in these nerves. Piper's original measurement was 123 m./sec. for human myelinated nerve, but this is generally agreed to be too high a value, and most other workers give results which range around 65 m./sec. (Munniel [58], Helmholtz [33], Alevek, Schaffer). In a man of average stature the nervous pathways to and from the cord had a length of about 120 cm., and the time taken for the disturbance to travel this distance will be 0·018 sec. In Snyder's [82] analysis of his results he gives the following estimated values :—

Nerve conduction	10
Synapse time	3
Receptor and effector latency	3·6
Total latency.. ..	16·6

and explains the discrepancy between this figure and his observed value for the latent period (11·3) as being due to modifications introduced by unassessed factors. It is clear that here he has taken the higher figure of Piper, 120 m. sec., for the velocity of the disturbance in nerve, giving a nerve time of about half the above estimated value. The latency of effectors and receptor is generally accepted to be in the neighbourhood of 3 σ (3·6 σ is the figure taken by Snyder).

The synapse time for other reflexes cannot be given as a value whose estimation is independent of the above measurements, as it has invariably been estimated from experiments which have involved nerve conduction and hence the values obtained are dependent upon the assumed rate of conduction in nerves. For similar reflexes widely differing values have been obtained, e.g., for the masseteric reflex 1σ (P. Hoffmann [36]), and $2\ \sigma$ (Jolly [45]), and for the Achilles reflex $8\ \sigma$ (F. A. Hoffmann [35]).

Taking as correct in each case the smallest values which have been suggested as the result of properly controlled experiments, we see that for the knee-kerk to be reflex in nature appears to demand an interval of $3 + 1 + 10 = 14\ \sigma$ between the stimulus and the response.

Comparisons between Latent Periods of Knee-jerks with that of the Contraction in Response to other Forms of Stimuli.

The contraction of the quadriceps femoris which has been held to follow mechanical stimulation whether directly of the muscle (Reinhard [69]), or of the skin around the patella [44], have both shown a delay in onset which is very definitely greater than that of the knee-jerk.

The only other form of stimulus of which the results have been recorded and measured is electrical stimulation over the motor point of the muscle. Forster, in 1897, claimed that the latent period of this response was greater than that of the knee-jerk; Dodge [16] found the reverse from his measurements. If Snyder's value of 2·5—3·6 for the latent period of direct stimulation is reliable it is obviously very much shorter than any delay recorded or suggested for the tendon-jerk.

A Comparison of the Latent Period of the Knee-jerk with that of other Muscle Reflexes in Man and in Animals.

One of the earliest studies of reflexes with which comparison was made was the wink reflex in response to electrical stimulation of the conjunctiva. Exner and Waller both measured this and found that the latent period was 57—66 σ and 50 σ respectively. Subtracting the conduction time and direct muscle latency from his figures, Exner concluded that the reduced reflex time lay between 47 and 55 σ. At the time when this result was published this value was smaller than the value for the latent period of the knee-jerk, but since more accurate measurement has shortened the latter figure so much it is now well above the accepted value, and falls into line with the other skin reactions in showing a delay which is characteristically big in comparison with that of the tendon phenomena.

Dodge found that the latency of the Achilles jerk was 11—18 σ greater than that of the patellar jerk, and agrees with other workers in ascribing these differences to the variations in length of the conducting paths. The same explanation is advanced by P. Hoffmann [36] to account for the shorter latent period of the knee-jerks in children (14—17 σ).

Of other animals where the knee-jerk has been measured the frog gives values of 11·4 σ (Jolly [45], and 15 σ (Dodge [16]); the rabbit 8 σ (Waller [90], and 22 σ (Scheven); and the cat 6·6 σ in spinal and 9·1 σ in decapitate preparations (Jolly [45]). The "reduced latency," i.e., synapse time, has been estimated by Jolly as being 3·7 σ for a frog and 1·8 σ for a spinal cat.

The smallness of these figures in comparison with those from man are probably due to the comparative shortness of the peripheral nervous pathways in spite of the fact that the velocity of conduction within these pathways is less. Jolly has also compared the latency of ipsilateral and cross extension reflexes and finds a difference of 1·4 σ, which he explains as due to diminished intraspinal pathway in the case of the ipsilateral response.

The other muscle-stretch reflexes the latency of which may be compared with that of the knee-jerk, are those from the masseter given by P. Hoffmann as 7 σ and from the Achilles tendon 22—44 σ (F. A. Hoffmann).

APPENDIX III.

The Tendon-jerk and other Muscle Responses.

Since contractions may be observed in most muscles to follow direct percussion over the main contracting mass, a comparison of such responses with the phenomena with which we are properly dealing may be expected to throw light upon the reflex or local nature of these last.

Reinhard in 1884 published [69] some observations upon this subject in which he came to the following conclusions:—

The tendon-jerk is most often a contraction of the whole muscle—referred to as the "total" response; that which follows local percussion is often a partial swelling limited to the neighbourhood of the blow—the "local" response.

The local response requires a stronger stimulus and varies considerably with its magnitude; the total contraction more rapidly reaches a maximum with increase of the stimulus and may then irradiate to other muscles.

In distinction, the local response persists during physiological sleep and that due to narcotics; in the latter condition less stimulus is required to elicit it.

In post-epileptic states the total contraction becomes harder to elicit or disappears; the local response remains unaffected.

Whereas in spastic limbs the local response is hardly visible and the total contraction much exaggerated, the reverse obtains in some flaccid cases as in tabes dorsalis.

In the early stage of atrophic paralysis the total contraction alone is often increased in facility; later it becomes much diminished, and the local response subject to much increase with changes in the electrical reactions. After death the total contraction begins to show diminution in one minute, and usually does not survive forty to sixty minutes; the local response is more facile in the first two hours, and does not disappear usually under five to six hours.

That the local effect is peripheral, direct muscular response is shown by its survival after curare.

Salomonson [94], working with a string galvanometer, has by this means divided muscular contraction into three groups:—

(1) Simple twitches preceded by a single action current.

(2) Those showing an irregularly alternating current of action.

(3) Those with no current of action.

The tendon responses he finds come into the first group; voluntary movements, epileptic and myoclonic convulsions into the second; muscle spasms, as in spasticity, tetanus and veratrine poisoning into the third.

Both of these workers, therefore, produce evidence to suggest that the tendon reflexes are essentially different from muscular contractions known to have a purely local origin.

APPENDIX IV.

A Discussion of Available Methods of Study.

When a muscle is thrown into increased activity it tends to contract. The mechanical changes which this entails are an approximation of its two ends and a thickening of its crossed section. Associated with the tendency to shorten is the development of tension, and with the tendency to thicken is an increase in the hardness or resistance to compression. Any of these quantities may be recorded separately but not entirely independently. Changes in length and tension development

may be produced and measured with a considerable degree of mutual independence and approximation to isotonic and isometric records.

It is more difficult to separate changes in thickness and resistance to compression; changes in length of the muscle have previously always been recorded as secondary changes produced in the relative disposition of the limb segments to which the muscle is attached and which are moved when it contracts. Changes in its thickness have been recorded as the movements produced in some rigid lever pressed against the body of the muscle and raised as the cross section and resistance to compression—i.e., its "hardness,"—increased.

The complex structure of the muscles used and their disposition in the body allow of no accurate correlation between thickening and shortening records either in their general form or in their time relations. In those obtained by leading from some segment of the limb acted upon by the contracting muscle the additional factors introduced by the inertia and momentum of the part moved, the unknown participation of the other muscles acting upon the same part, especially of the physiological antagonists, and the necessity for the conversion of an angular into a linear movement, are all difficulties which prevent the resulting curves from being comparable with the direct shortening curves of detached muscle.

"Shortening" Method.

No record of the shortening of the muscle has been made apart from the movements of the leg thereby produced, and it is obvious that the presence of the attached passive mass of bone and soft tissues must profoundly modify the course of the contraction. Its moment of inertia will retard the onset of shortening and increase the apparent latent period—during the active contractions it will cause a lag proportional to its mass and correspondingly great because of the high mechanical disadvantage at which the muscle acts: the cessation of contraction and onset of relaxation will be altogether masked by the angular momentum of the parts and their final arrest under gravity or other restoring forces tending towards the original position of resting equilibrium. Many attempts have been made to minimize these effects. Thus Bowditch and Warren had their subject lying upon his side with the whole leg supported by a series of trapezes so that it moved entirely in a horizontal plane: a position which did not alter in any way the distorting effect of the inertia of the system moved, but lessened the effect of gravity.

There have been very many records taken by means of a string or wire, etc., attached to the foot. Bechterew used a rigid lever hinged to an anklet clasped about the leg and resting at its other end against a tambour. Tuttle, as late as 1924 [87], used a wire from the heel; Lombard [48] recorded the excursion of the foot in a similar manner, and also made use of a long lever fixed to the skin over the patella which moved with the tilting of this bone as the knee became further extended. In order to get some value for the latent period, most observers have employed a delicate electrical contact so placed, e.g., behind the heel, that it is broken immediately the knee begins to extend. The result of such observations has been to provide a number of comparable values for the latent period but no comparable records of the course of the contraction. It should be noted that whether records are taken from the foot, the leg, the patella or the belly of the muscle, so long as contraction entails a displacement from rest of the lower leg the records will be subject to the distortion outlined above—delayed by inertia at their commencement and prolonged by pendular overthrow before their cessation.

"Thickening" Method.

The thickening of the muscle on contraction has been recorded in various ways. Dodge [16] recorded the movements of a spring pressed lightly against the skin over the thigh. Purves Stewart [68] employed the breaking of a circuit in which were included aluminium rods fixed to the skin and tilting with deformity due to swelling of the muscle. Sternberg [83] used a tambour fixed round the thigh with pneumatic connections to a stylus. Rosenhein strapped on to the surface of the skin over the quadriceps a piece of apparatus containing a two-point electrical contact which was broken by stretching of the strap against an adjustable spring when the muscle swelled. Many observers such as ter Meulen [85], Jarisch and Schiff [42] and others as early as Brissaud [13], used these and differing pieces of apparatus for recording the same change.

It is clear that the results of such experiments cannot be compared with those of other methods, or even *inter se*, except in respect of the latent period, and even here the correspondence cannot be expected to be very exact. If one could reasonably assume that the whole thigh is deformed simultaneously and proportionally with the change in thickness of the underlying muscle; that the shortening marches *pari passu* with the thickening or even commences at the same instant; that the

whole muscle thickened simultaneously and to a proportionate degree throughout its length, then a greater degree of correspondence might be anticipated. Of all these unjustifiable assumptions the least unjustifiable is that which supposes a simultaneous commencement of shortening and thickening—to this extent then values obtained for the latent period may be compared with those obtained from shortening experiments.

Another discrepancy arises from the fact that when stimulated the muscle may harden or change its cross-section shape without any decrease in length. Since no shortening can occur until the inertia of the parts to which the ends of the muscle are attached is overcome, the latent period of hardening would be expected to be less than that of shortening, and this is generally the case.

To note the sequence in which thickening appears at a number of arbitrarily selected points on the thigh and to deduce from this sequence the course of the wave of excitation which must have passed among the muscle fibres beneath these points, can have no validity.

A study of the physical factors involved shows that there can be no correspondence expected between the time relations of shortening and of proportionate degrees of thickening, for, considering the muscle to be a roughly ellipsoidal shaped mass of constant volume and the whole of its substance to be equally contractile, we see that the relation between changes in the longitudinal and any transverse diameter invoked by a change in shape of the muscle in the direction of a more spherical form is given by $4/3.\pi x^2 y = k$, when x = maximum cross-section diameter, y = longitudinal diameter, k = some constant, i.e., $y = 3k/4\pi x^2$, or $dy/dx = -3k/2\pi x^3$, so that as x, the thickness, increases, the rate of decrease of y, the length, falls off considerably. Hence the relation between the shortening and the thickening varies considerably, and the shortening per unit increase of thickness decreases rapidly as the muscle becomes thicker.

Finally it must be allowed that shortening and lengthening are the changes whereby the muscle functions in the body, while thickening and hardening are concomitant changes which are determined secondarily by purely physical conditions. Each muscle is designed so that it can most advantageously pull upon its tendon when its component fibres shorten, and in measuring shortening we are measuring the essential change to which all parts of the muscle contribute proportionately. In recording thickening we are sampling some arbitrary cross-section across which the various muscle fibres will probably be contributing very differently to all but maximal thickening effects, and such maximal thickening we know never occurs in reflex contractions.

APPENDIX V.

Measurement of the Curves.

Some of the records here included were obtained by leading a string direct from the patellar support, round a pulley and on to a stylus which scribed against a moving smoked surface. This method was discarded as soon as it became obvious that the distortions introduced by this apparatus obscured the essential characters of the curve of contraction. Some of the results so obtained are, however, given below, as the record could be run for a much longer time than was possible with a photographic plate falling at the same speed. Some effects, and notably that of continued clonus, were more easily demonstrated in this way.

Curves obtained with Graphical Recording.

The only features of these curves which reproduced the undistorted contraction of the muscle with sufficient fidelity to justify their measurement were the relative height of successive responses and the rate of clonus when this occurred.

The normal curve obtained had the general form here reproduced, and the points from which measurement was made are indicated upon the diagram (fig. 3).

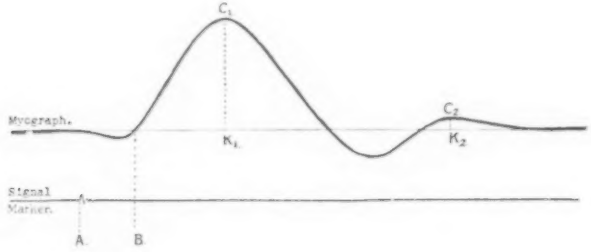


Fig. 3.—A diagram of the normal knee-jerk as obtained with the graphic method of recording, indicating the points from which measurements were made. (Read from left to right.)

For continued clonus the intervals between successive contractions are K_1, K_2, K_3, K_4, K_5, K_6, etc. Some of the curves at the end of this paper are reproduced as tracings from the varnished smoked-paper records, others as photographs of these records themselves.

Curves obtained with Photographic Recording.

The general form of the curves has been previously described.

The characteristics of each curve selected for measurement were those which could be seen to vary from patient to patient, and also those which from a theoretical consideration could be expected to be of significance. The points O, X, A, B, C, D, from which measurement was made, are indicated upon the diagram (fig. 4).

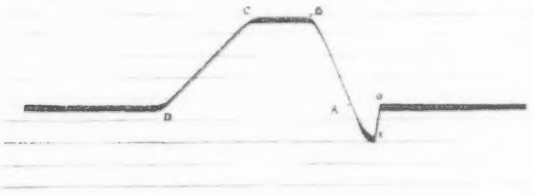


Fig. 4. A diagram of the normal knee-jerk as obtained with the photographic method of recording, indicating the points from which measurements were made. (Read from right to left.)

The vertical distances on the record provide a magnification of the actual distances moved through by the patella. The magnification for each record was determined by comparing the width of the bar fixed to the recording needle with that of its shadow. This ratio gave a factor for the reduction of all vertical distances on the plate into corresponding distances at the patella.

Horizontal distances were reduced to time intervals by comparison with the shadow cast by a tuning-fork vibrating 100 times per second. Since it could not be assumed that the plate fell in the camera with uniform speed, each distance had to be compared with the time-marker shadows immediately beneath it. This was done by using a double-microscope comparimeter with which to compare selected points on the curve with others on a fixed millimetre scale. Every fifth indentation of the time-marker shadow was then similarly given values from the same scale and the requisite intervals evaluated.

The Latent Period.

The moment of incidence of the blow upon the patella was not measured by the making of an electrical circuit in most of the records, because this involved not only the unknown latency of the recording mechanism but also the time taken for compression of soft tissues when

these necessarily intervened between the instrument and the rigid patella. It was found that the moment of stretch was so abruptly marked upon the records that its measurement to within 1σ was reasonably accurate.

The selection upon the records of the moment of commencement of reflex muscular contraction presented the greatest difficulty in the estimation of this quantity—the latent period.

The instrument adjusted in position upon the patient's leg presented the condition of two elastic bodies in equilibrium, the stretched muscle and the extending spring. In the absence of any additional forces applied to this system, e.g., that supplied by the physiological response investigated, the displacement of the point of application of these two opposing forces in the direction of the spring should lead, when released, to a damped oscillation of the system about the point of equilibrium. The only really satisfactory means of determining the moment of entry into this field of the additional force—that supplied by the reflex muscular contraction—is to obtain records from this system both with and without the reflex present, and after superimposition of these two records to determine the point at which one departs from the other—this point can then be taken as indicating the moment at which the muscle contraction commenced.

In practice this can only rarely be done. Since with identical conditions the procedure employed either does or does not give rise to contraction of the quadriceps, it follows that two such curves cannot ever be obtained. On those occasions on which, without altering any of the conditions under control, identical stimuli gave at one time no response, and, on repetition, a definite contraction—and these were not rare, but occurred quite fortuitously—the immediately obvious assumption had to be made that one of the many uncontrollable factors: attention, internal inhibition or facilitation, changes in tonic innervation, etc., had become altered.

The alternative was to obtain a series of records under conditions of variation of one controllable factor, e.g., by using various grades of initial tension designedly insufficient for the eliciting of a reflex, and then by extrapolation of the results obtained, where consistency justified this, to deduce a theoretical "base line" upon which to apply the curve obtained after the tension had been raised sufficiently for the muscle response to appear. The results obtained from measurement of the curves, taking at the moment of onset of the muscular contraction a point of obvious discontinuity in what should be a smoother curve—

where this point was not otherwise explainable—have yielded fairly constant results, and results in accord with those obtained by other observers in this field, as far as the normal response is concerned.

The horizontal distance between O and X, where O is the moment of onset of stretch-stimuli and X the moment of discontinuity as above defined, has to be compared with the distance between the underlying time-marker shadows. If this distance be O X, and D the distance between the first and last of the ten time-intervals recorded immediately below, then the latent period is $= \frac{OX \cdot 100}{D} \sigma$.

The Slope of the Ascent.

The curve of ascent was in all normal cases rectilinear for the greater part of its extent. Its lowest part was concave upwards as contraction commenced, and it was slightly rounded off at the top where it merged with the plateau. It would have been a convenience had these departures from the linear form been sufficiently small to be neglected, and the highest point B sufficiently well defined so that the co-ordinates of points required for other measurements could be used also in this determination. Unfortunately this was rarely so, and in all cases the slope of the rising phase was determined by measuring the co-ordinates of two points as far apart as possible upon the perfectly rectilinear part of this curve. These figures were used, by reduction of the magnification and comparison with the time marked, to find the slope in terms of millimetres displacement of the patella per sigma interval of time.

The height of the contraction was taken as the ordinate distance between A and B where A was the point at which the rising curve cut the base-line and B the highest point attained by that rise. It is given after reduction of the magnification in terms of millimetres displacement of the patella.

The duration of the plateau in sigma intervals was obtained from the horizontal distance from B to C; C being the point of greatest discontinuity as the plateau merged into the curve of relaxation. In most normal cases, C was quite a sharp definite point on the curve, and determined with greater ease than when the descent was delayed by the addition of a hump or preliminary convexity upwards.

The total duration of the response was taken arbitrarily at the time interval (in sigma) between A and C. In physiological records the beginning of this period is generally measured from the commencement

of the electrical response. It was felt that since such electrical records were not here available it was better to measure from A rather than from O or X. This avoided including in the duration time the latent period and provided two easily defined points from which to measure time intervals which were comparable for the different curves but not equivalent to the "duration of the response" as usually defined.

The slope of the fall.—In normal cases the curve of relaxation commenced abruptly at a well-defined angle and was thereafter linear or concave upwards. The only way in which the characteristic angle of slope could be determined in each case was, as in the ascent, to take two arbitrary points as far apart as possible on the strictly rectilinear part of the curve and by the appropriate magnification-reduction and time-marker comparison of their co-ordinates, to arrive at a value for the slope in terms of millimetre displacements of the patella per (sigma) unit of time.

EXAMPLES OF RECORDED RESPONSES.

1.	Normal knee-jerks	Figs. 5-8
2.	Hypertonic knee-jerks from spastic patients	Figs. 9-14
3.	The clonic knee-jerk from spastic patients	Figs. 15-20
4.	Hypotonic knee-jerks from patients with cerebellar disease	Figs. 21-22
5.	The knee-jerk in extrapyramidal (Parkinsonian) rigidity ..	Figs. 23-25
6.	The knee-jerk in chorea—the sustained knee-jerk	Figs. 26-27
7.	Illustrations of the effect of reinforcement efforts	Figs. 28-29

The myograph records (white on black) are to be read from left to right, the optically recorded curves (black on white) from right to left.

FIGS. 5-7.—Responses from healthy subjects.

FIG. 5.—Initial tension 400 gm. Time marker (above) 1·5 sec.
Signal (below) stimulus.

FIG. 6.—Initial tension 600 gm. Time marker below 1/100 sec.

FIG. 7.—Initial tension 400 gm. ,, ,, ,, 1/100 sec.

FIG. 8.—A series of responses from a normal, healthy person. The curves have been traced one above the other so that the moments of stimulation lie along the same ordinate. The six lines below are marked each in intervals corresponding to 1·5 sec., and are numbered in accordance with the curves to which they apply.
The initial tension was the same in each case.
The distortion of the spring hammer before release was increased progressively from below upwards; the figures in brackets are proportional to the degree of distortion in each case.
N.B.—These curves illustrate the observation that with increasing strength of the blow given at this constant initial tension the height of the curve of contraction is also increased.

FIGS. 9-14.—Responses from patients with clinical spasticity.
Time marker 1/100 sec.
These curves are typical of those obtained from persons with pyramidal tract lesions. The ascent is usually abrupt, the plateau well marked, the angle obscured by the upward convexity of the first part of the descent upon relaxation and the later parts of the descent are prolonged or interrupted by secondary contractions of varying force.

FIG. 9.—G. J. A case of disseminated sclerosis. Spastic paraplegia well marked. Initial tension 300 gm. Descent almost complete, slight clonic contraction.

FIG. 10.—B. B. Hemiplegia. Considerable spasticity of left leg. Left leg recording. Initial tension 700 gm. Descent interrupted by secondary contraction.

FIG. 11.—A. H. A patient with spinal tumour. Great spasticity of both legs. Initial tension 150 gm. The curve of relaxation shows a well marked preliminary hump with later secondary contractions.

FIG. 12.—W. P. Cerebral syphilis. Spasticity of the legs with ankle clonus. Initial tension 200 gm. Convex descent and secondary contraction.

FIG. 13.—C. C. Left hemiplegia. Spasticity of left limbs. Left leg recording. Initial tension 300 gm. Time marker not included. A secondary contraction delays the later part of the descent.

FIG. 14.—The same patient as in fig. 13. Initial tension 500 gm.

FIGS. 15-20.—Responses from spastic patients illustrating the development of clonus with increasing initial tension.

Figs. 16-20 were taken from the patient J. D. who then showed well-marked spastic paraplegia and from whom a spinal tumour in the upper dorsal region was later removed.

FIG. 15.—W. B. Spinal tumour. Spastic paraplegia.
Time marker below in 1 5 sec., separate for each curve. The fraction in small figures at the beginning of each record indicates by its denominator the force of the blow and by its numerator the initial tension. From these it will be seen that the blow remained constant throughout while the initial tension was progressively increased, i.e., 250, 300, 400, 500 gm. The moment of stimulation lies in each case vertically above the small indicator arrow. Permanent clonus was established at 500 gm. I.T.

FIG. 16.—Initial tension 150 gm.

FIG. 17.—Initial tension 300 gm.

FIG. 18.—Initial tension 500 gm.

FIG. 19.—Initial tension 600 gm.

FIG. 20.—Initial tension 600 gm. For this record the photographic plate was allowed to fall at a much lower rate than for the previous records in order that the regularity and permanence of the series of clonic beats might be demonstrated.

FIGS. 21-22.—Records illustrating the characteristics of the responses from patients with hypotonicity of the limbs, i.e., the sigmoid character of the curves of contraction and relaxation, the absence of any true plateau, the rounding-off of the terminal "angle," the relatively abrupt nature of the descent from the apex of contraction, and the frequency with which the curve falls, upon relaxation, slightly below the original resting base line.

FIG. 21.—D. C. Cerebellar tumour. Left side. Hypotonicity of the limb musculature suggested by ease of passive manipulation and facility of passive displacement from defective postural fixation. The hanging knee-jerk was pendular in character Left leg recording. Initial tension 400 gm.

FIG. 22.—I. A. Cerebellar tumour. Hypotonicity with pendular knee-jerks. Right leg recording. Initial tension 150 gm.

FIGS. 23-25.—Records illustrating the characteristics of responses obtained from patients with extra-pyramidal (Parkinsonian) rigidity, i.e., the rounding-off of the plateau, the absence of the "angle," the relatively slow relaxation, the long delay shown in the return of the base-line to the original resting level.

FIG. 23.—W. F. Right leg recording. Initial tension 300 gm.

FIG. 24.—E. S. Right leg recording. Initial tension 300 gm.

FIG. 25.—M. C. Right leg recording. Initial tension 250 gm.

FIGS. 26-27.—Records illustrating the characteristics of the responses obtained from patients with chorea rheumatica, i.e., the hypotonic character and the sustained knee-jerk. Time marker (below) indicates 1/100 sec.

FIG. 26.—G. N. Hypotonicity with choreic postures and movements. The knee-jerks normally obtained were sometimes sustained in character. Right leg recording. Initial tension 600 gm.

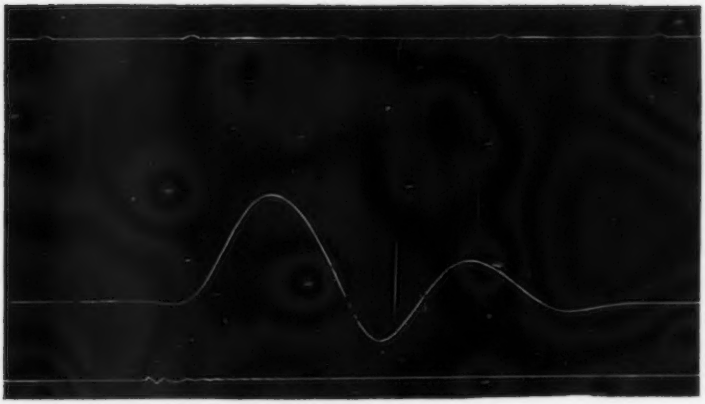


FIG. 5.

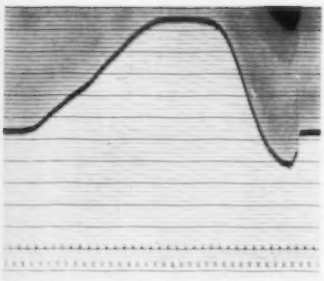


FIG. 6.

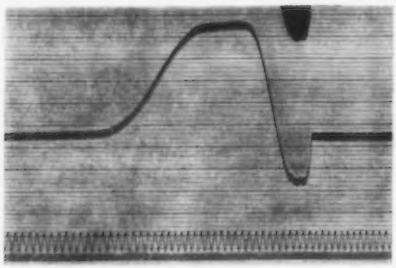
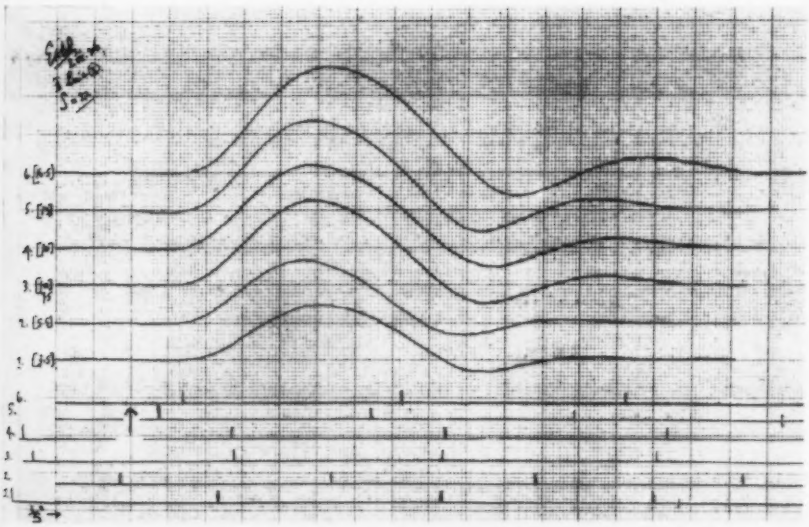


FIG. 7.



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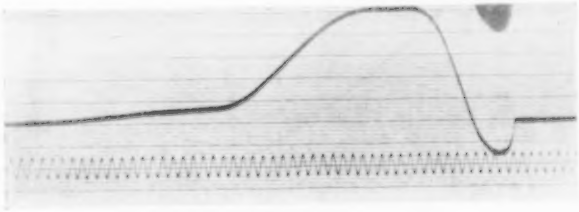
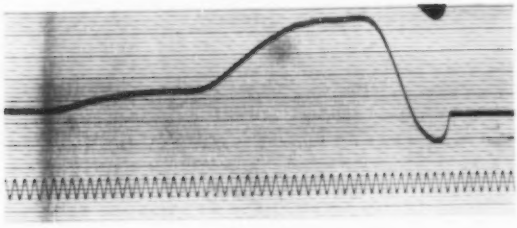


FIG. 9.



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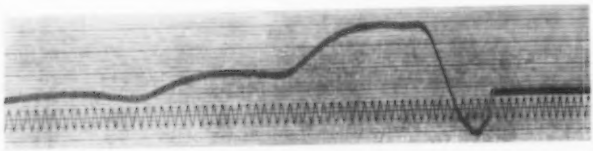
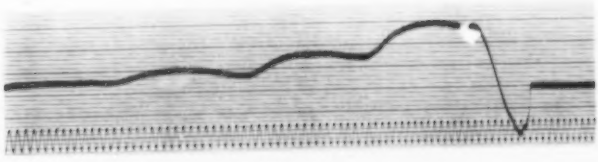


FIG. 11.



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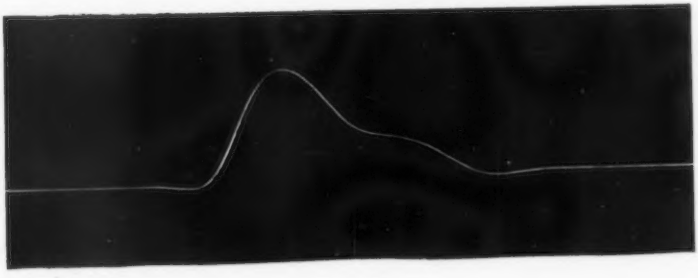
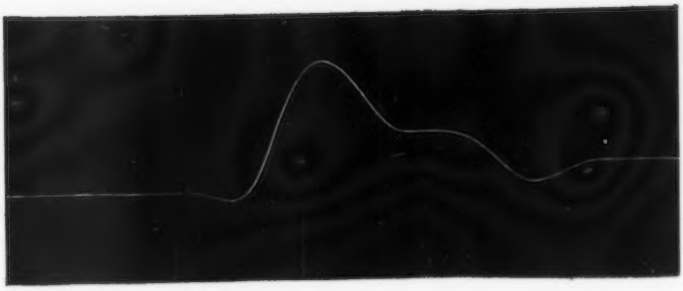


FIG. 13.



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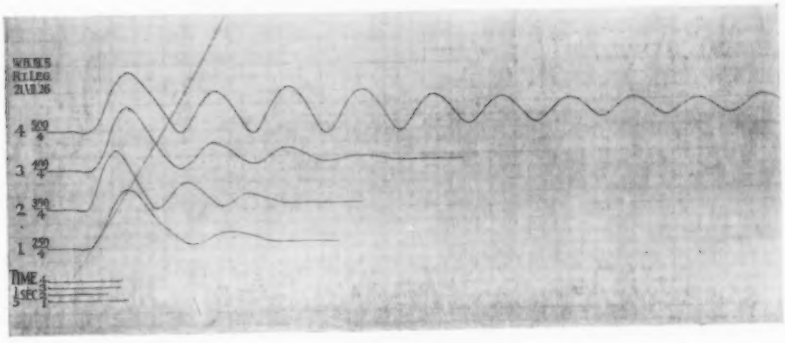


FIG. 15.

FIG. 16.

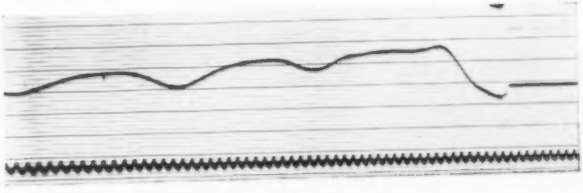
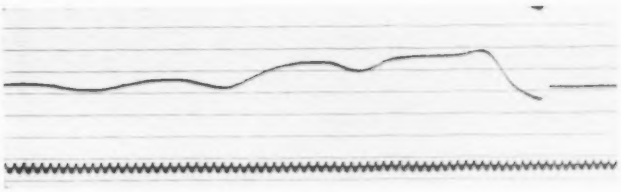


FIG. 17.



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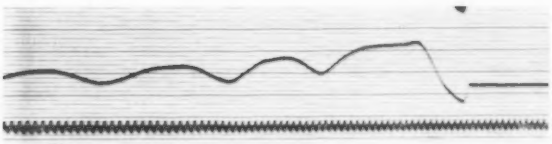


FIG. 19.

FIG. 20.

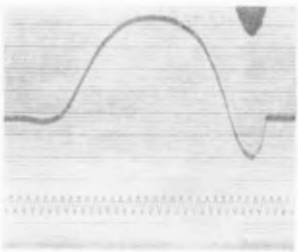


FIG. 21.

FIG. 22.

Fig. 23.

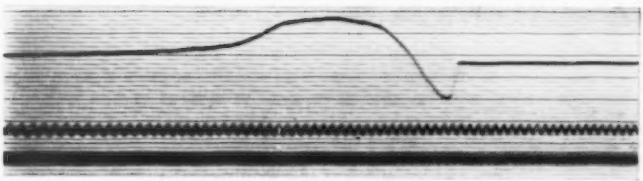


Fig. 24.

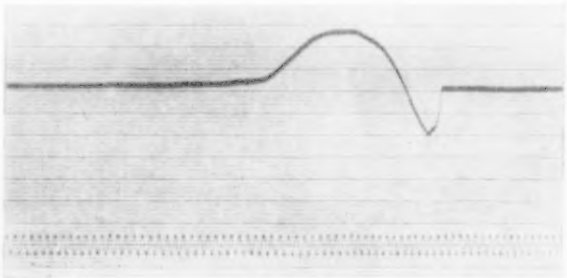
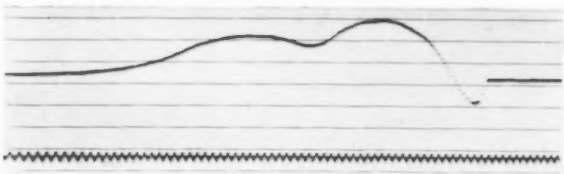


Fig. 25.



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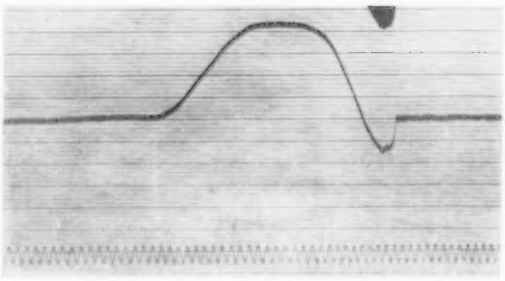

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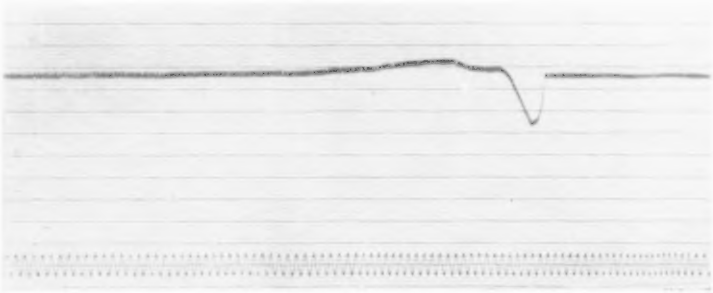

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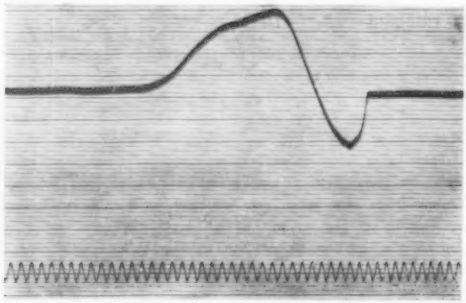

FIG. 29.

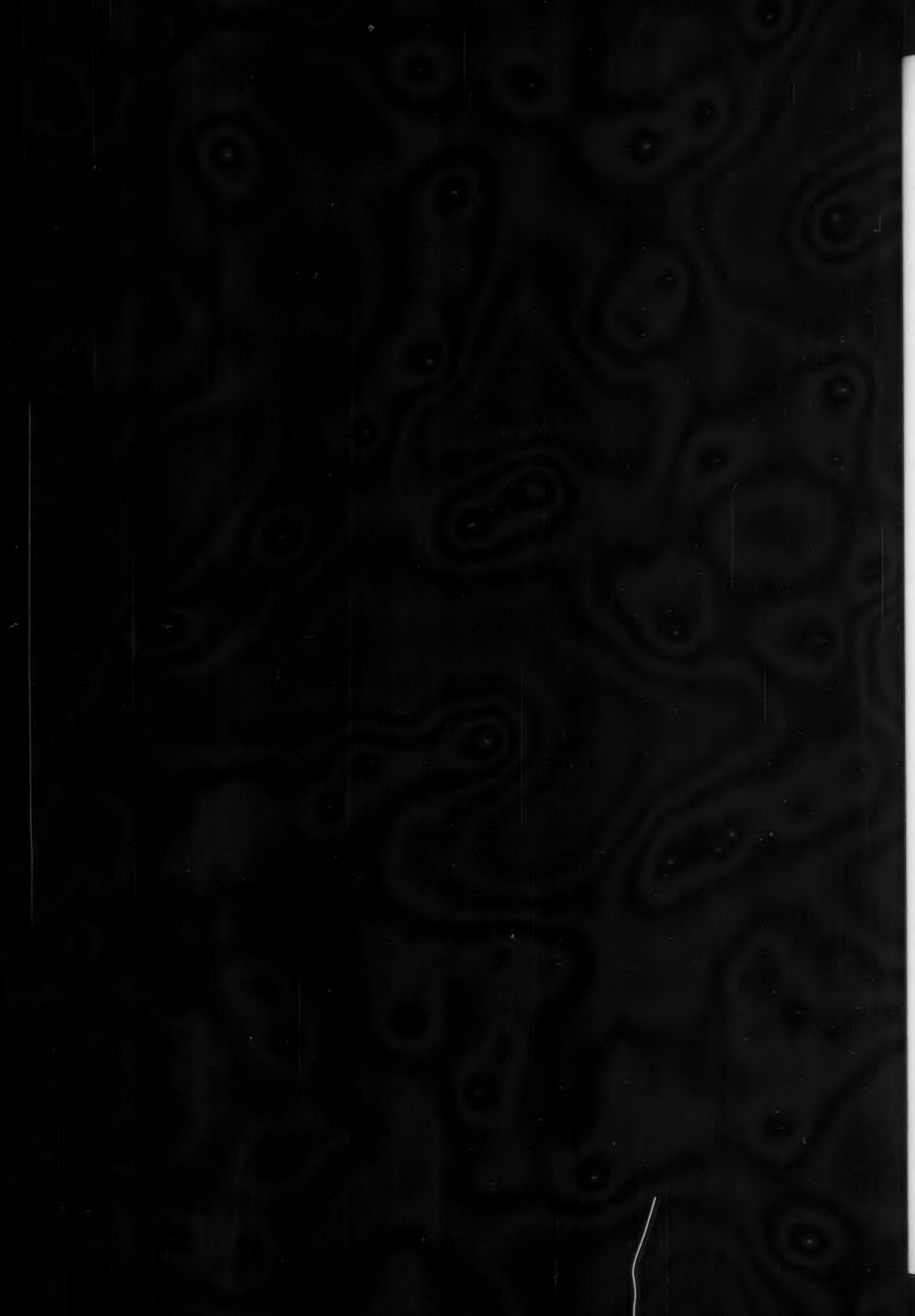

FIG. 27.—V. D. No clinical hypotonicity but some choreic movements. The knee-jerks were sometimes sustained. No records of prolonged after-contraction were obtained from this patient. Initial tension 500 gm.

FIGS. 28-29.—Records illustrating the effect of "reinforcement efforts" upon the facility of eliciting the knee-jerk. Time marker (below) indicates 1/100 sec.

FIG. 28.—A. F. Healthy person. Right leg recording. Initial tension 250 gm. Strong blow delivered. A very slight response recorded.

FIG. 29.—The same patient as in fig. 28. Initial tension 250 gm. Clenching of hands requested just before the blow was given, to be maintained during the recording. The same blow was given as in record fig. 28. A clear response of good amplitude resulted.

TABLE I.

A comparison between the minimal initial tensions required for eliciting a response from (*a*) normal } persons.
(*b*) spastic }

Patient	Condition	Minimal initial tension
I. A. ..	Cerebral tumour	100
J. D. ..	Spinal tumour	100
G. J. ..	Disseminate sclerosis	200
W. H. ..	Spino-cerebellar ataxy	200
H. P.-S. ..	Hemiplegia	150
A. W. ..	Disseminate sclerosis	200
F. H. ..	Hemiplegia	200
P. M. ..	Amyotrophic lateral sclerosis ..	150
R. B. ..	Normal	400
W. B. ..	Neurasthenia	300
H. B. ..	Cervical rib	300
Z. C. ..	Cerebellar tumour	400
A. C. ..	Normal	350
W. C. ..	Normal	300
B. P. ..	Normal	350
B. R. ..	Normal	400
I. D. ..	Normal	300
F. D. ..	Normal	350

This shows that in spastic cases with increased facility of the response the minimal effective initial tension is lowered.

TABLE II.

Illustrating the effect of variations in (*a*) initial tension,
(*b*) force of blow,
upon the amplitude of the response.

I. T. = initial tension in grammes weight.
S. = a number obtained from the setting of the apparatus which indicates the degree of distortion of the spring-hammer before release. The numerical values of these figures is in inverse proportion to this degree of distortion, i.e., the smaller the number the greater the blow delivered.
C_1K_1 = height of the plateau in millimetres above the base line.

Patient, M. T. Ward I, bed 14. Spastic paraplegia.
6.vii.26. Left leg recording.

Record	I. T.	S.	C_1K_1
1 ..	150 ..	3 ..	7·5
2 ..	150 ..	5 ..	16
3 ..	150 ..	7 ..	20
4 ..	150 ..	10 ..	22
5 ..	200 ..	7 ..	17
6 ..	200 ..	7 ..	17
7 ..	250 ..	3 ..	7·5
8 ..	250 ..	5 ..	14
9 ..	250 ..	7 ..	17
10 ..	300 ..	5 ..	12
11 ..	300 ..	7 ..	15

This table shows that for this patient the amplitude of the response within this range of values is increased by increasing the force of the blow.

TABLE III.

Measurement of a series of curves.

N_1N_2.—These values represent distances measured upon the curves in millimetres and not time intervals between the corresponding parts of the contraction recorded—the smoked surface was not in all cases travelling at the same rate. The rate of clonus was arrived at by using the last curve (12) and evaluating the distances here given in terms of time intervals by comparison with the time marker.

K_1K_2, K_2K_3, &c., refer to points upon the curve as in text figure 3.

Patient, C. B. Ward VII, bed 19. Disseminate sclerosis.
26.vii.26. Right leg recording.

Curves K_1K_2	1	2	3	4	5	6	7	8	9	10	11	12
K_1K_2 ..	57	49	45	55	55	53	55	50	53	52	47	38
K_2K_3 ..		43	41	45	44	43	44	39	40	44	38	23
K_3K_4 ..	—	—	38	37	36	33	31	29	33	37	28	25
K_4K_5 ..	—	—	—	—	—	35	40	37	37	38	38	25
K_5K_6 ..	—	—	—	—	—	—	—	—	37	40	35	25
K_6K_7 ..	—	—	—	—	—	—	—	—	40	40	30	24
K_7K_8 ..	—	—	—	—	—	—	—	—	38	40	30	24
K_8K_9 ..	—	—	—	—	—	—	—	—	—	40	31	24
K_9K_{10} ..	—	—	—	—	—	—	—	—	—	—	30	27
$K_{10}K_{11}$ ..	—	—	—	—	—	—	—	—	—	—	29	25
$K_{11}K_{12}$ ..	—	—	—	—	—	—	—	—	—	—	28	29
$K_{12}K_{13}$ ..	—	—	—	—	—	—	—	—	—	—	27	25
$K_{13}K_{14}$ ..	—	—	—	—	—	—	—	—	—	—	—	28
$K_{14}K_{15}$ ..	—	—	—	—	—	—	—	—	—	—	—	29
$K_{15}K_{16}$ ..	—	—	—	—	—	—	—	—	—	—	—	28
$K_{16}K_{17}$ ..	—	—	—	—	—	—	—	—	—	—	—	27
Time marker 1/5 sec. ..	68	64	65	68	64	64	68	65	68	68	62	60

TABLE III (*continued*).

Curve	1 250	2 350	3 400	4 500
K_1K_2 ..	78	57	67	67
K_2K_3 ..	—	57	54	57
K_3K_4 ..	—	—	55	56
K_4K_5 ..	—	—	—	55
K_5K_6 ..	—	—	—	53
K_6K_7 ..	—	—	—	51
K_7K_8 ..	—	—	—	49
K_8K_9 ..	—	—	—	50
K_9K_{10} ..	—	—	—	49

TABLE III (*continued*).

Curve	1 250	2 350	3 400	4 500
Distance in 2/5 sec. : time interval K_1K_2 ..	121	95·5	114·5	119·5
Time interval K_1K_2 : distance in 2/5 sec ..	0·26	0·24	0·23	0·22
Distance in 2/5 sec. : time interval K_2K_3 ..	—	104	119	122
Time interval K_2K_3 : distance in 2/5 sec ..		0·22	0·18	0·185
Distance in 2/5 sec. : time interval K_3K_4 ..			120·5	124
Time interval K_3K_4 : distance in 2/5 sec. ..			0·18	0·18
Distance in 2/5 sec. : time interval K_4K_5 ..			—	124
Time interval K_4K_5 : distance in 2/5 sec. ..				0·18
Distance in 2/5 sec. : time interval K_5K_6 ..				124
Time interval K_5K_6 : distance in 2/5 sec. ..				0·17
Distance in 2/5 sec. : time interval K_6K_7 ..				126
Time interval K_6K_7 : distance in 2/5 sec. ..				0·16
Distance in 2/5 sec. : time interval K_7K_8 ..				128
Time interval K_7K_8 : distance in 2/5 sec. ..				0·15
Distance in 2/5 sec. : time interval K_8K_9 ..				130
Time interval K_8K_9 : distance in 2/5 sec ..				0·15
Distance in 2/5 sec : time interval K_9K_{10} ..				130
Time interval K_9K_{10} : distance in 2/5 sec. ..				0·15

TABLE IV.

Illustrating the effect of increase of the Initial Tension upon—
The height of the contraction,
The permanency of the clonus,
The degree of relaxation during clonus.

N.B.—I.T. = initial tension in grammes weight.
C_1K_1 = amplitude of the response in millimetres above the base line.
H = height of the partial relaxations of clonus above the original resting level.

Patient, C.B. Ward VII, bed 19. Disseminate sclerosis.
26.vii.26. Right leg recording.
Drum record.

Curve	I.T.	C_1K_1	Number of after-beats	H.
1	150	1·85	1	—
2	200	2·3	2	0·2
3	250	2·4	3	0·2
4	300	3·0	3	0·4
5	300	3·1	3	0·5
6	350	3·1	4	0·75
7	400	3·1	4	0·75
8	450	3·2	5	0·75
9	450	2·9	7	1·0
10	500	2·6	8	1·0
11	600	3·4	permanent clonus	1·75
12	625	3·6	,,	2·5

Patient, W. B Ward III, bed 15. Right hemiplegia.
21.vii.26. Right leg recording.
Drum record.

Curve	I.T.	C K	Number of after-beats	H.
1	250	4·5	1	—
2	350	4·5	2	0·75
3	400	4·8	3	1·0
4	500	4·5	permanent clonus	1·5

This table illustrates the observation that with a constant blow increase of the Initial Tension—
Increases the height of the contraction,
Increases the number of clonic after-beats,
Raises the level of contraction upon which clonus is established.

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